CORSO SUPERIORE SIFO IN FARMACIA CLINICA

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Appunti di galenica pediatrica

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“I bambini non sono piccoli adulti quando prendono un farmaco. Le modalità di assunzione, l’assorbimento, il metabolismo e l’escrezione dei farmaci nel bambino sono diversi da quelli dell’adulto. Questi fattori non sono costanti, ma variano con l’età. La maggioranza dei farmaci nel mondo non sono stati messi in commercio per essere somministrati ai bambini”

Rapporto congiunto UNICEF-OMS Essential Medicines for Children

Agosto 2006

Di cosa parleremo

1. Aspetti fisiologici del bambino
2. le formulazioni pediatriche e gli eccipienti
3. Il gusto
4. Approccio ad alcuni casi clinici

Alcune osservazioni

- I piccoli pazienti possono presentare sostanziali differenze rispetto all'efficacia del farmaco:
  - Per i cambiamenti del corpo dovuti alla crescita
  - Per i cambiamenti metabolici
  - Per i cambiamenti funzionali di alcuni organi
  - Per la/le patologia/e concomitanti

…ancora osservazioni…

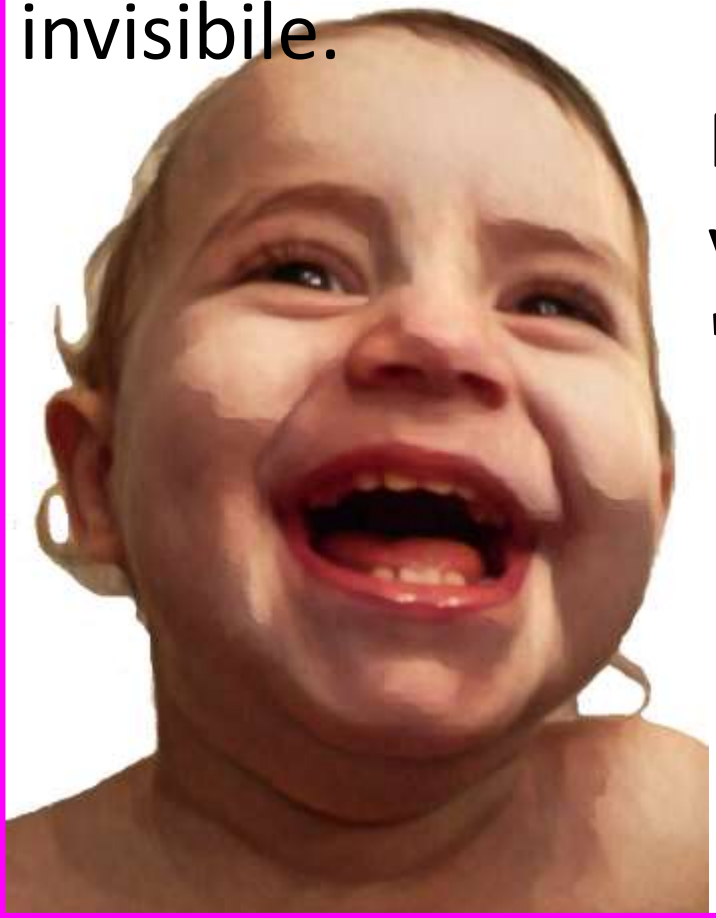
- Generalmente la posologia del farmaco nel bambino è espressa in mg/kg, ma sempre più spesso si osserva mg/BSA
- Il bambino cresce, e il dosaggio del farmaco?
- Anche la diluizione dei farmaci per uso ev/im nei bambini molto piccoli può essere di difficile gestione
- La forma farmaceutica migliore è quella che il bambino accetta di prendere ed è in grado di farlo.

…e poi…

- Se pensiamo ad un esempio: generalmente i farmaci a rilascio modificato non sono stati “pensati” prendendo in considerazione il tratto GI del bambino
- la palatabilità è un aspetto importante per la compliance dei piccoli pazienti… ma non solo…
- La somministrazione del farmaco è un “lavoro per due” (genitore e figlio)

"Non cammina ancora? Dice così poche parole? Non sa neanche scrivere il suo nome?!“

"No, non ancora... però può disegnare un sole **verde** e un prato **blu**, può sconfiggere mostri e credere nelle fate, gioca con un cane parlante e ascolta un amico invisibile.



Può anche avere poteri magici e vivere in un mondo incantato.“

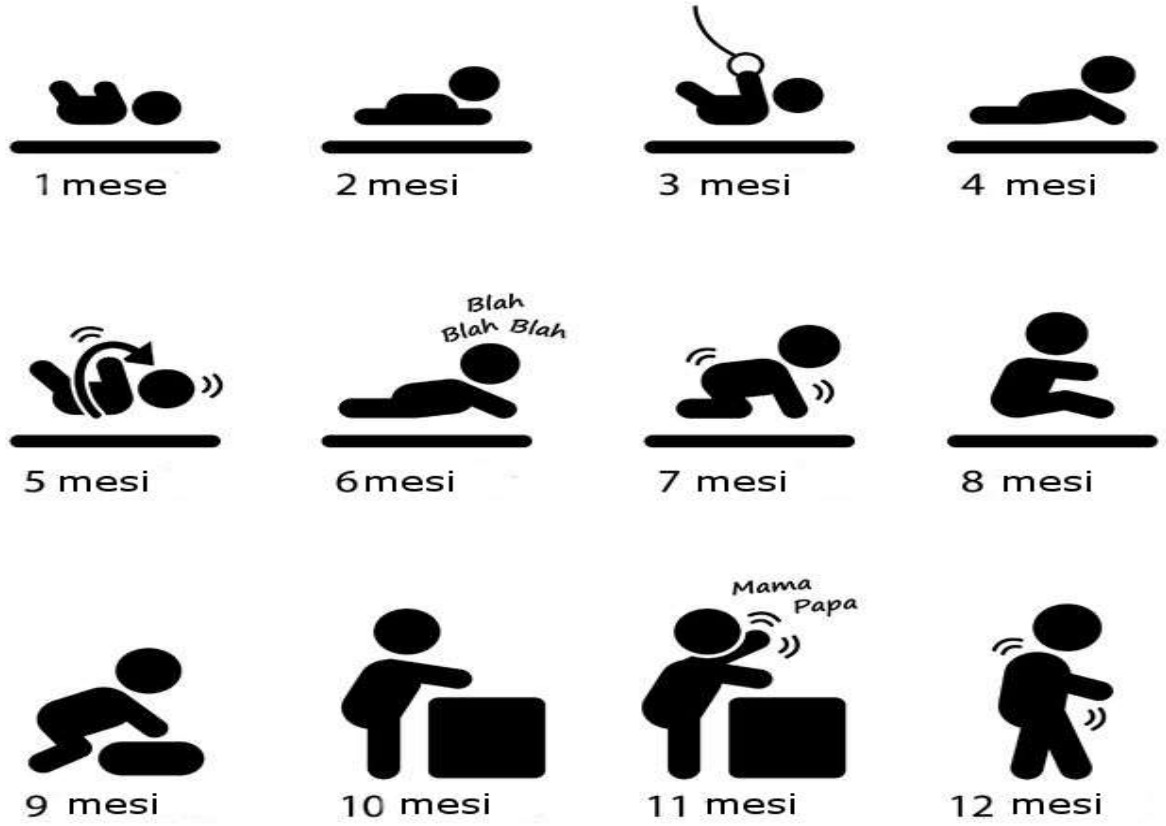
"E quindi cosa sa fare?“

"Sa fare il bambino. E sa (di) essere speciale."

STIAMO LAVORANDO PER LUI!

Farmacologia dal neonato all' adolescente

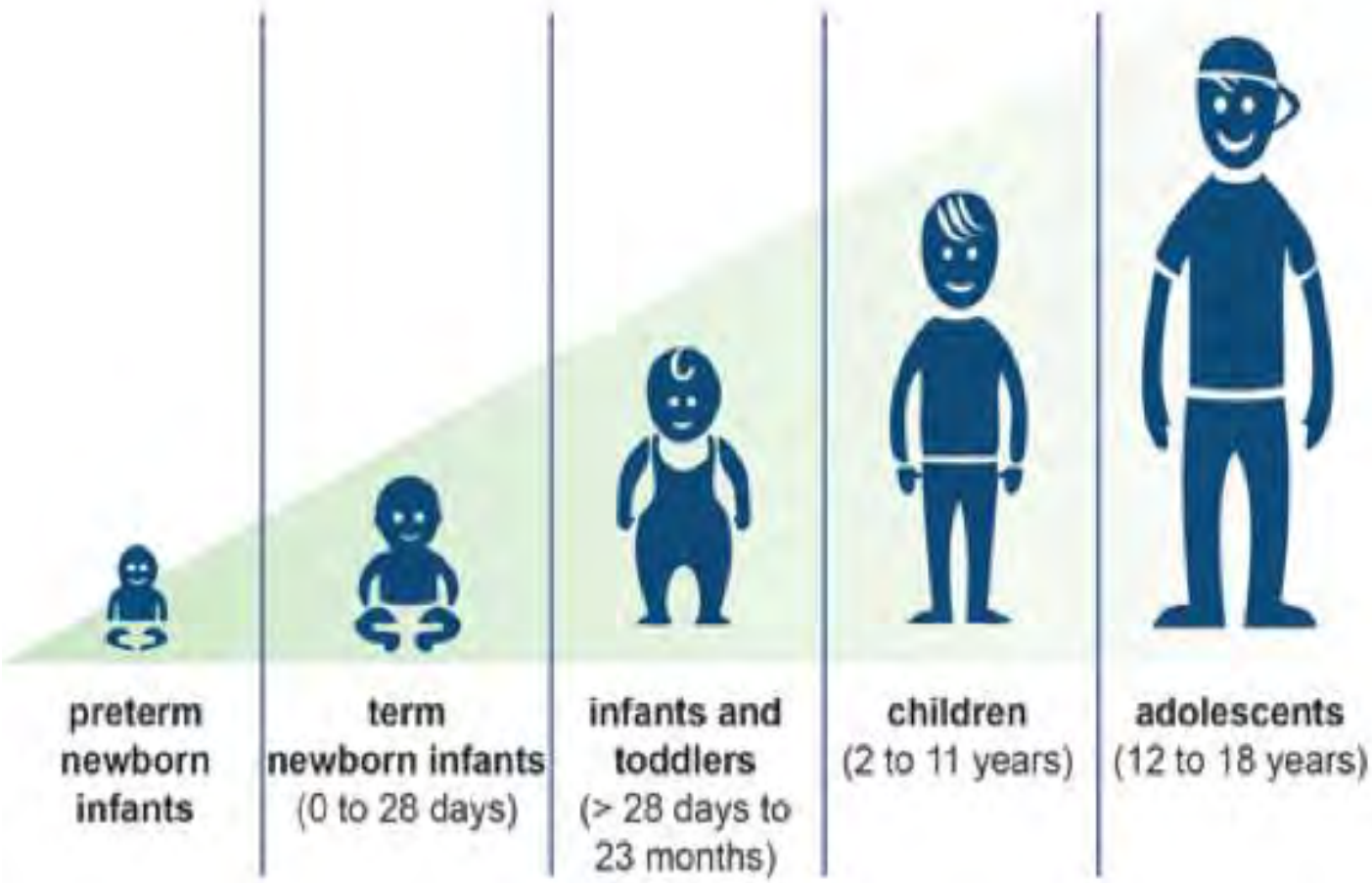
E’ necessario individuare le differenze farmacocinetiche e farmacodinamiche tra il paziente pediatrico e il paziente adulto affinché la farmaco-terapia nel bambino risulti efficace e sicura



Indice

A. Stadi dello sviluppo
B. Farmacocinetica: ADME nel bambino
C. Sperimentazione Clinica stato dell'arte
D. La legge e i Farmaci Off Label

5 Stadi dello Sviluppo



Le implicazioni farmacologiche sono comunque più estese nei primi anni di vita causa i molteplici cambiamenti :

- Aumento di peso: raddoppia nei primi 5 mesi e triplica entro il primo anno.

- Aumento di altezza: del 50% durante il primo anno e raddoppia entro i 4 anni.

- La superficie corporea (BSA): raddoppia entro il primo anno di vita per triplicare entro il 4.

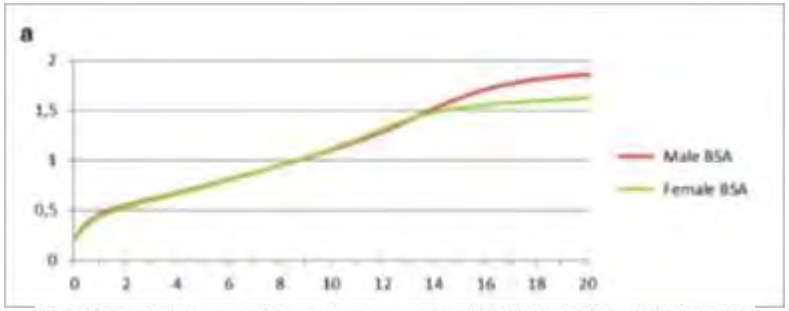
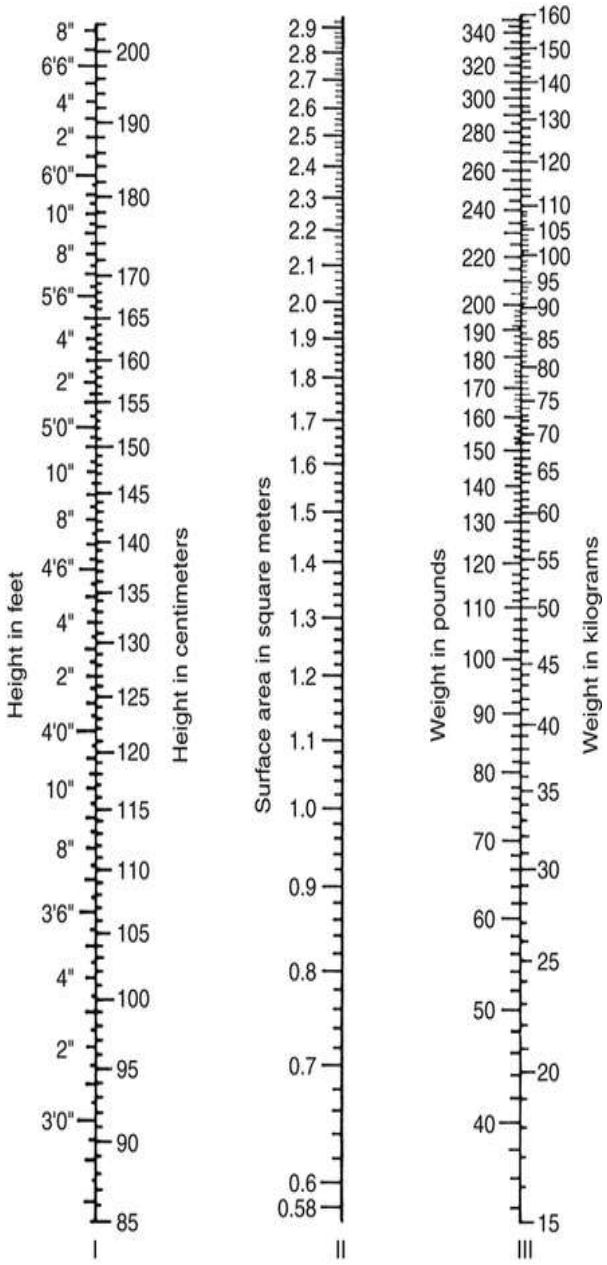


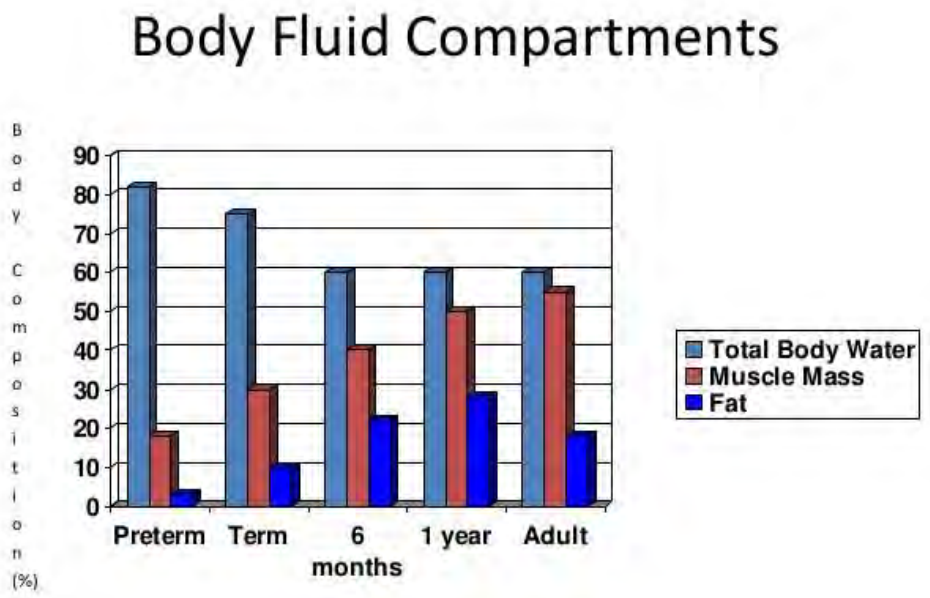
Fig. 2.3 Growth in humans; BSA and body mass index (BMI) [Data: CDC and World Health Organisation (WHO); BMI = weight (kg)/(height (m))^2; BSA calculation based on the Mosteller formula ($BSA = (W \times H/3600)^{1/2}$)]. **(a)** BSA curve for males and females 0–20 years of age. **(b)** BSA



•L’acqua corporea totale: 85% del peso di un pretermine e 70-75% del peso di uno a termine. Al 60% entro i primi 4 mesi.

• I grassi: 3% del peso in un pretermine e il 12% di uno a termine. Raddoppia entro i 4-5 mesi.

• La massa proteica: aumenta fino ai valori adulti



Farmacocinetica (FC)

Valutando i parametri farmacocinetici i pazienti pediatrici possiamo distinguerli in:

•Bambini con età ≥ 2 anni: FC può essere prevista dai dati ottenuti dall'adulto applicando le differenze date dai modelli farmacocinetici.

•Bambini con età < 2 anni: FC differente da quella adulta.

Differenze Farmacocinetiche tra bambino e adulto

ABSORPTION

- Gastric pH higher (less acidic); by 3 years, acid per kg of body weight similar to adults
- Gastric emptying is slowed; reaches adult levels in 6–8 months

METABOLISM

- Liver immature; does not produce enough microsomal enzymes
- Older children may have increased metabolism, requiring higher dosing

EXCRETION

- Kidney immaturity affects glomerular filtration rate and tubular secretion
- Decreased perfusion rate of the kidneys
- Renal clearance reaches adult values after 2 years

DISTRIBUTION

- Total body water (TBW) 70% to 80% in full-term infants, 85% in premature newborns, 64% in children 1 to 12 years, similar to adults (greater TBW means fat content is lower)
- Decreased level of protein binding
- Immature blood-brain barrier

Immature functions

Overview of developmental features that can affect pharmacokinetics		
Developmental feature	Relevant age period	TK implications
Chemical absorption		
Increased oral absorption of certain agents (e.g., metals)	birth through weaning	potential for greater chemical uptake
Greater dermal absorption	primarily in premature neonates	potential for greater chemical uptake
Greater inhalation rate per respiratory surface area	birth through several years	potential for greater local dose in respiratory tract
Body composition	birth through 3 months	less partitioning and retention of lipid soluble chemicals; larger volume of distribution (V_d) for water-soluble chemicals
Lower lipid content		
Greater water content		
Larger liver weight/body weight	birth–6 years but largest factor in first 2 years	greater opportunity for hepatic extraction and metabolic clearance; however, also greater potential for activation to toxic metabolites
Immature enzyme function	birth–1 year but largest factor in first 2 months	slower metabolic clearance of many drugs and environmental chemicals; less metabolic activation but also less removal of activated metabolites
Phase I reactions		
Phase II reactions		
Larger brain weight/body weight; greater blood flow to CNS; higher BBB permeability	birth–6 years but largest factor in first 2 years	greater CNS exposure, particularly for water-soluble chemicals which are normally impeded by BBB; larger V_d
Immature renal function	birth–2 months	slower elimination of renally cleared chemicals and metabolites
Limited serum protein binding capacity	birth–3 months	potential for greater amount of free toxicant and more extensive distribution

Assorbimento

Dipende dalla via di somministrazione:

1. Orale
2. Cutanea
3. Intramuscolare e Subcutanea
4. Rettale
5. Inalatoria

Somministrazione Orale

Da preferire in quanto:

- Economica
- “Facile” preparazione e personalizzazione
- Meno traumatizzante per il bambino

Differenze dell’apparato gastrointestinale

Table 2.2 Age-dependent factors affecting gastrointestinal absorption and the resultant pharmacokinetic outcomes relative to adult levels

	Newborn	Neonate (1 day to 1 month)	Infant (1 month to 2 years)
Physiological factor			
Gastric pH	Neutral → 1	>5	Adult
Gastric emptying	Reduced (variable)	Reduced (variable)	Increased
Intestinal surface area	Reduced	Reduced	Adult
Intestinal transit time	Reduced	Reduced	Increased
Pancreatic and biliary function	Very immature	Immature	Adult
Bacterial flora	Very immature	Immature	Adult
Enzyme/transporter activity	Very immature	Immature	Adult
Pharmacokinetic outcome			
Rate and extension of absorption	Variable	Variable	≥Adult
Gastrointestinal first-pass effect	Very reduced	Reduced	Approaching adult

1. pH Gastrico

Adulto: pH ≈ 1-2
Neonato: pH > 5

Entro un mese raggiunge i valori dell' adulto.

Neonati a termine: secrezione acide aumentano già nelle primissime ore di vita

Pretermine: processo più lento

Alterazione della stabilità e del grado di ionizzazione del farmaco → variazione del grado di assorbimento del farmaco

I PPIs

acid secretion. Pharmacokinetics studies have shown that the half-life of omeprazole and lansoprazole, the two PPIs indicated and most commonly compounded into suspensions for children, is shorter in children than in adults.

The hard gelatin capsule containing omeprazole or lansoprazole remains intact during its brief transit through the esophagus and dissolves in the stomach acid to release granules of its prodrug. The granules' polymer coating dissolves only at a pH greater than 6, allowing release of omeprazole in the alkaline duodenum where its mechanism of action takes place. Releasing the prodrug in the acidic conditions of

While omeprazole or lansoprazole are indicated for use in children, some differences occur between the two. In a 2000 study conducted by Sharma et al, the effectiveness of capsule versus suspension forms of the two PPIs was tested. Results showed that compounded lansoprazole suspension raised intragastric pH to levels that were comparable to those seen with the intact capsule formulation. The effect of omeprazole suspension on intragastric pH was quantitatively smaller than that observed with the intact capsule formulation.[8]

Rx LANSOPRAZOLE 3-MG/ML SUSPENSION

For 100 mL

Lansoprazole 30-mg capsules		10 capsules
Sodium bicarbonate		8.4 g
Purified water	qs	100 mL

METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Place the sodium bicarbonate in a large beaker with sufficient purified water to dissolve.
4. Empty the lansoprazole capsules into the beaker that contains the sodium bicarbonate and purified water.
5. Allow the mixture to set and mix well.
6. Pour the mixture into a graduated cylinder and bring to volume with purified water.
7. Pour the mixture back into the beaker and mix well.
8. Pour the suspension into amber oval bottles.
9. Cap, seal, and label.

PACKAGING

Package in tight, light-resistance containers.

LABELING

Keep out of reach of children. Use only as directed. Shake well.

STABILITY

A beyond-use date of 28 days at refrigerated temperature can be used for this preparation.

Rx OMEPRAZOLE (SIMPLIFIED) 2-MG/ML SUSPENSION

For 100 mL

Omeprazole 2-mg capsules		10 capsules
Sodium bicarbonate		8.4 g
Purified water	qs	100 mL

Note: As an alternate, sodium bicarbonate injection may be used instead of powder and purified water.

METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Place the sodium bicarbonate in a large beaker and add a small amount of water.
4. Mix the solution well until dissolved.
5. Empty the omeprazole capsules into the beaker that contains the sodium bicarbonate and purified water.
6. Mix the solution well until the powder is dissolved and a cream-colored suspension is formed.
7. Pour the mixture into a graduated cylinder and bring to volume with purified water.
8. Pour the mixture back into the beaker and mix well.
9. Pour the suspension into amber oval bottles.
10. Cap, seal, and label.

PACKAGING

Package in tight, light-resistance containers.

LABELING

Keep out of reach of children. Use only as directed. Shake well.

STABILITY

A beyond-use date of 48 days at refrigerated temperature can be used for this preparation.

Rx PANTOPRAZOLE SODIUM 2-MG/ML ORAL LIQUID

For 100 mL

Pantoprazole sodium		200 mg
Sodium bicarbonate 8.4% solution		50 mL
Purified water	qs	100 mL

METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Pulverize the pantoprazole sodium tablets to a fine powder.
4. Add the sodium bicarbonate solution and mix well.
5. Add purified water to volume and mix well.
6. Package and label.

PACKAGING

Package in tight, light-resistant containers.

LABELING

Keep out of reach of children. Use only as directed.

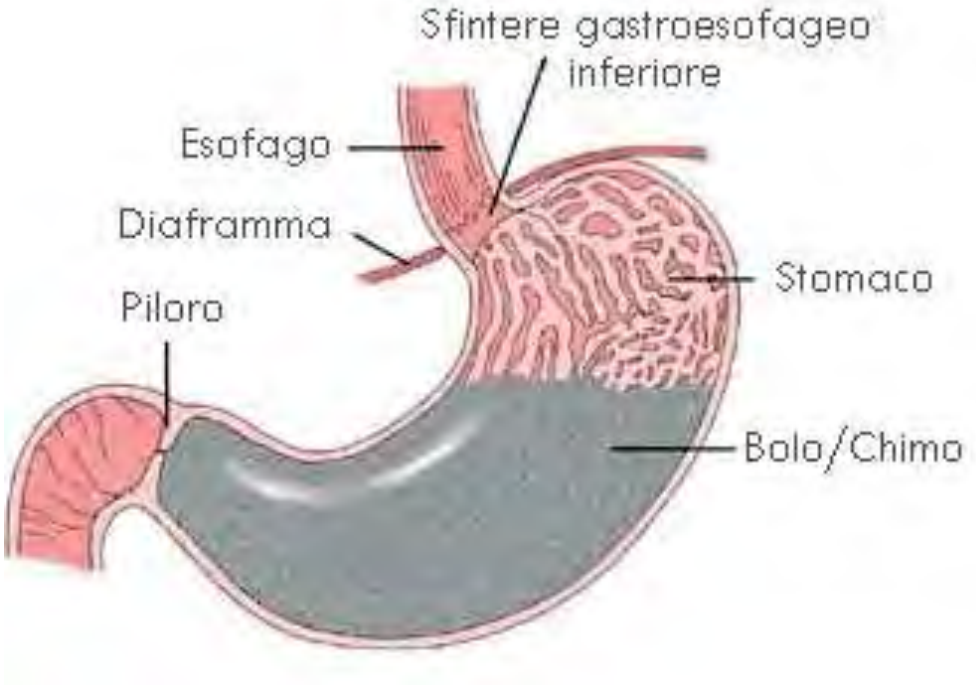
STABILITY

A beyond-use date of 14 days in a refrigerator and up to 90 days at -20°C has been used for this preparation.

2. [No author listed.] National Digestive Diseases Information Clearinghouse. *Heartburn, Gastroesophageal Reflux (GER), and Gastroesophageal Reflux Disease (GERD)*. NIH Publication No. 07-0882. [NDDIC Website.] May 2007. Available at: www.digestive.niddk.nih.gov/ddiseases/pubs/gerd/. Accessed January 10, 2011.
3. [No author listed.] The American College of Gastroenterology. *The Word on GERD: Understanding GERD*. [ACG Website.] 2006. Available at: www.gi.org/patients/gerd/wordLasp. Accessed on

2. Tempo di Svuotamento Gastrico

Intorno alle 6-8 ore
Le tempistiche si avvicinano al modello adulto al 6-8 mese



i.e.: pancrelipasi…

3. Motilità dello Stomaco

Irregolare

Tempo di transito maggiore nei primi 6 mesi (8-96 ore)

- ↑ Tempo di svuotamento gastrico
- Irregolarità della motilità gastrica

determinano

maggiore tempo di permanenza nello stomaco nel neonato:

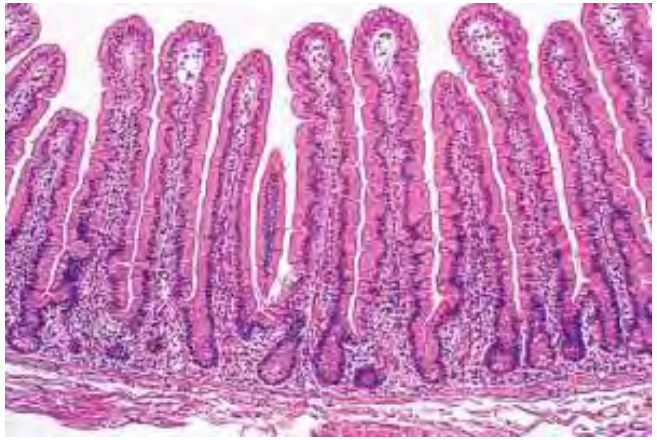
- Farmaci assorbiti a livello gastrico vengono assorbiti in maggior quantità
- Farmaci assorbiti a livello intestinale hanno un assorbimento ritardato

4. Superficie Intestinale

Ridotta

Supera in percentuale quella degli adulti

Variazione flusso sanguigno nelle prime 2-3 settimane → alterazione gradiente di concentrazione lungo la mucosa intestinale



5. Enzimi Gastrointestinali

Minore attività

↑ Biodisponibilità dei farmaci (dipende…)

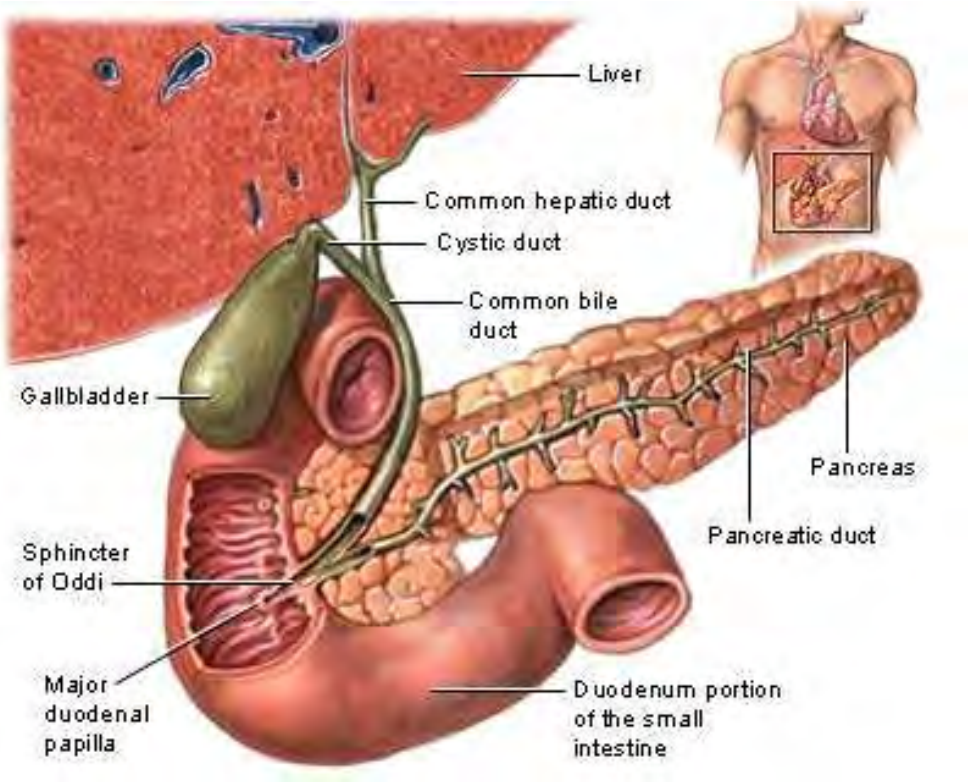
The CYP3A subfamily is a predominant gut wall enzyme, which is involved in the metabolism of more than 70% of currently administered drugs 29. CYP3A4 and CYP3A5 are present in abundance in the small intestine of adults, yet there are limited data regarding their expression in paediatric populations.

Metabolism in the gut lumen and wall can decrease the absorption of a wide variety of drugs including **ciclosporin,** **nifedipine** and **verapamil**…

6. Acidi Biliari ed Enzimi Pancreatici

Minore concentrazione rispetto l' adulto

↓ Assorbimento dei farmaci liposolubili



CompoundingToday.com
122 N Bryant Avenue, Edmond, OK 73034 | 800.757.4572 | 405.330.0094 | info@compoundingtoday.com

FORMULA NUMBER: 2794

FORMULA NAME: Rifampin 25-mg/mL in Cherry Concentrate and Syrup NF, Human, Veterinary

DOSAGE FORM: Syrup

FORMULA (Rx):

Ingredients	For: 100 mL			Lot#	RPh Initials
Rifampin		2.5	g	_____	_____
Cherry Syrup [HUMCO]	Concentrate	20	mL	_____	_____
Syrup NF (Simple Syrup)	qs	100	mL	_____	_____

SYNONYMS:
Rifadin; Rifadib; Rimactane; Rifater; Rifampicin

USE/TYPE:
Human Use
Veterinary Use
Non-Sterile Preparation

CATEGORY:
Amebicide
AntiMycobacterial
AntiProtozoal

NOTES:
Use disposable materials for the preparation as rifampin will dye or stain materials to an orange-red color including contac lenses. Capsules or tablets may be used for the preparation. Work with dispatch as riframpin is light sensitive.

SPECIALIZED EQUIPMENT:

METHOD OF PREPARATION:

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Triturate the powder from rifampin capsules or pulverize the tablets to a fine powder in a glass mortar.
4. Geometrically incorporate the cherry syrup concentrate and mix to a smooth suspension.
5. Geometrically add sufficient Syrup NF to volume and mix until uniform.
6. Package and label.

LABELING:
For Oral Use Only
Shake Well
Keep Out of Reach of Children

Inoltre…

Fino al 4 mese i sistemi di trasporto attivi e passivi sono immaturi perciò i farmaci vengono assorbiti più lentamente.

Diminuzione dell' eliminazione dei farmaci per effetto di primo passaggio poiché risulta diminuita l'attività degli enzimi di trasporto nel fegato.

Somministrazione Cutanea

L’ assorbimento aumenta rispetto l’ adulto:

- BSA/Peso corporeo più elevato rispetto l’adulto perciò neonato viene esposto a una maggior quantità di farmaco
- Pretermine: minor spessore dello strato corneo
- Infanti: estesa perfusione cutanea ed elevato grado di idratazione dell’ epidermide

[3]

Permeabilità cute di un Pretermine

Studio del 2004 ha riportato i tassi di permeabilità dei pretermine rispetto bambini nati a termine [4]:

- Pretermine prima della 30esima settimana: ↑ 100-1000 volte
- Pretermine dopo la 32esima settimana: ↑ 3-4 volte

Fenomeno di breve durata

Somministrazione Intramuscolare e Subcutanea

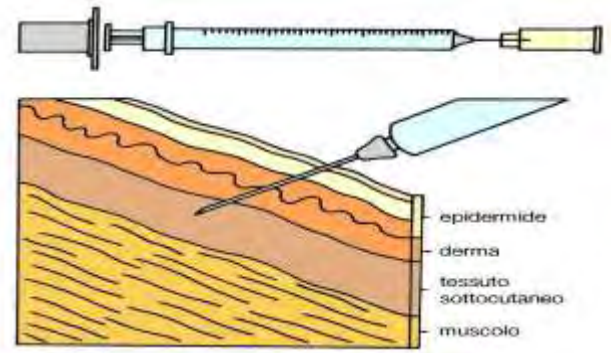
Da evitare

Assorbimento diminuito poiché:

- ↓ Perfusione sanguigna
- Inefficiente contrazione muscolare

[5]

Compensato da ↑ densità capillari a livello muscolare e scheletrico



i.e.: Benzilpenicillina benzatinica

Somministrazione Rettale

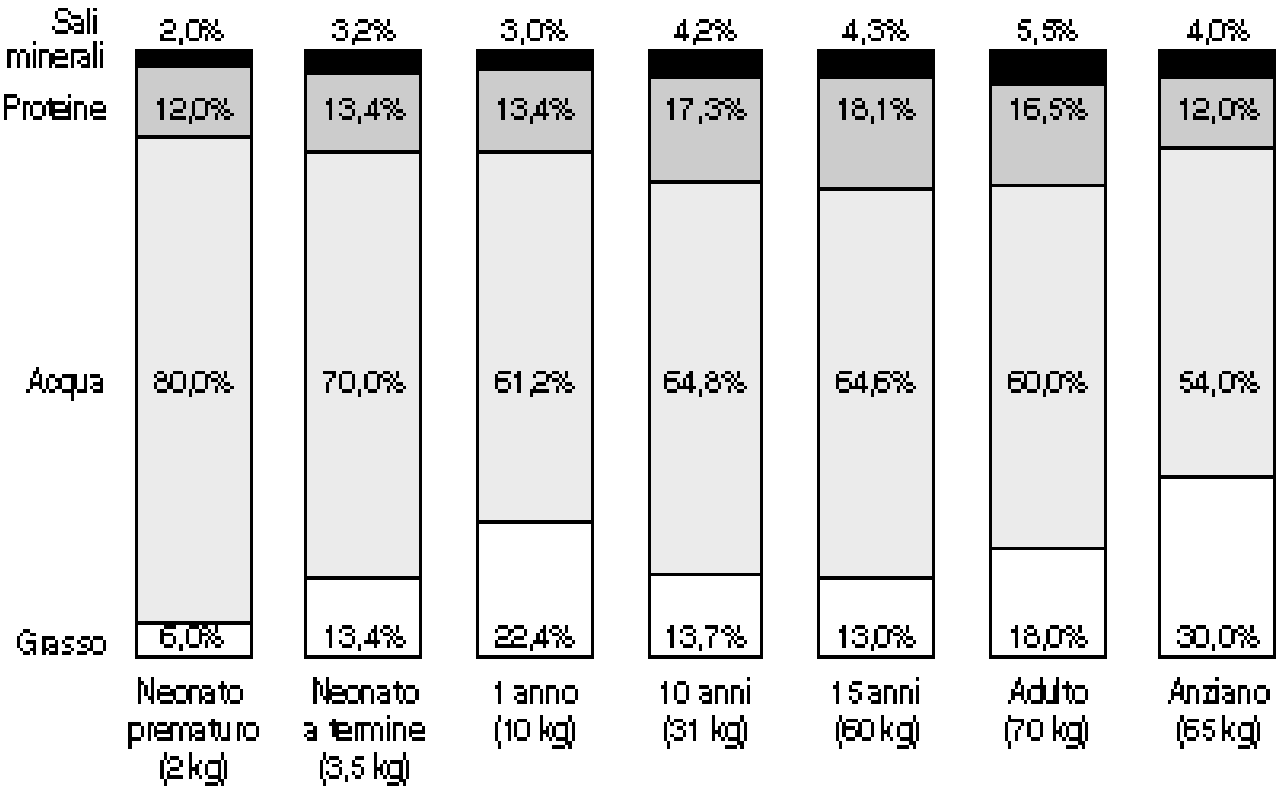
Elevato assorbimento:

- Alta perfusione sanguigna
- Metabolismo epatico immatura

Tuttavia neonati hanno maggior ampiezza delle contrazioni del retto → aumentata espulsione di farmaci solidi [6]

Distribuzione

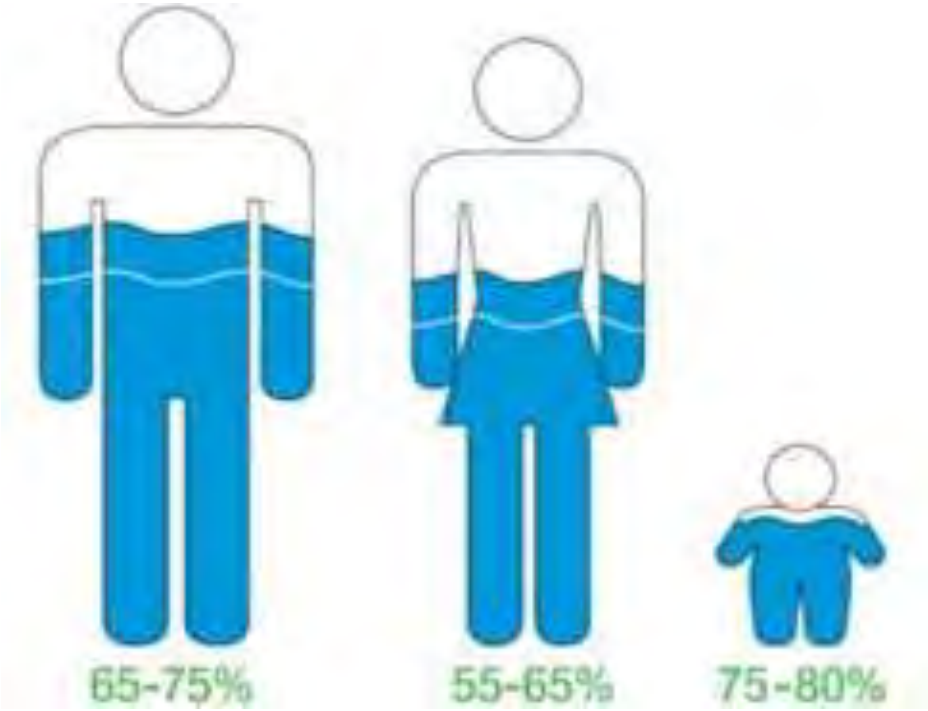
Si modifica parallelamente alla variazione della composizione corporea che avviene durante la crescita [7]



Acqua Corporea

70-75% del peso nei bambini a termine

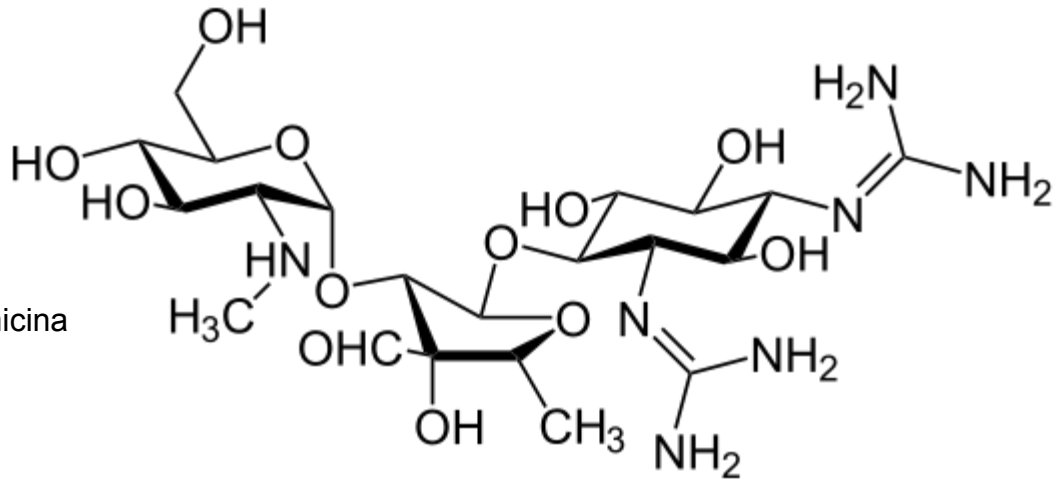
85% del peso nei bambini pretermine



Aminoglicosidi

Antibiotici idrosolubili che si accumulano nello spazio extracellulare

Acqua extracellulare nel bambino è 40% del peso corporeo → variazione della concentrazione di farmaco a livello dei recettori [8]



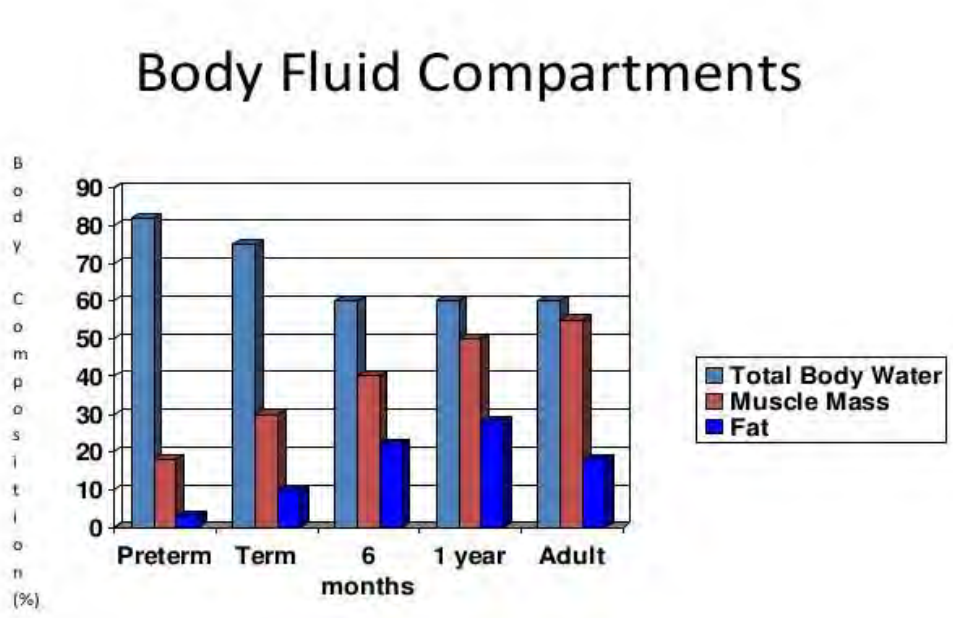
Streptomicina

Grasso Corporeo

Pretermine: 1% del peso corporeo

A Termine: 15% del peso corporeo

Minor accumulo di farmaci liposolubili



Legame alle Proteine Plasmatiche (PP)

Diminuzione quali-quantitativa per:

- ↓ concentrazione delle PP
- ↓ affinità di legame

[9]

Albumina fetale: ↓ capacità di legare farmaci

Presenza di sostanze endogene che competono con i farmaci per legarsi alle PP

Conseguenze

Aumento della concentrazione farmaco libero

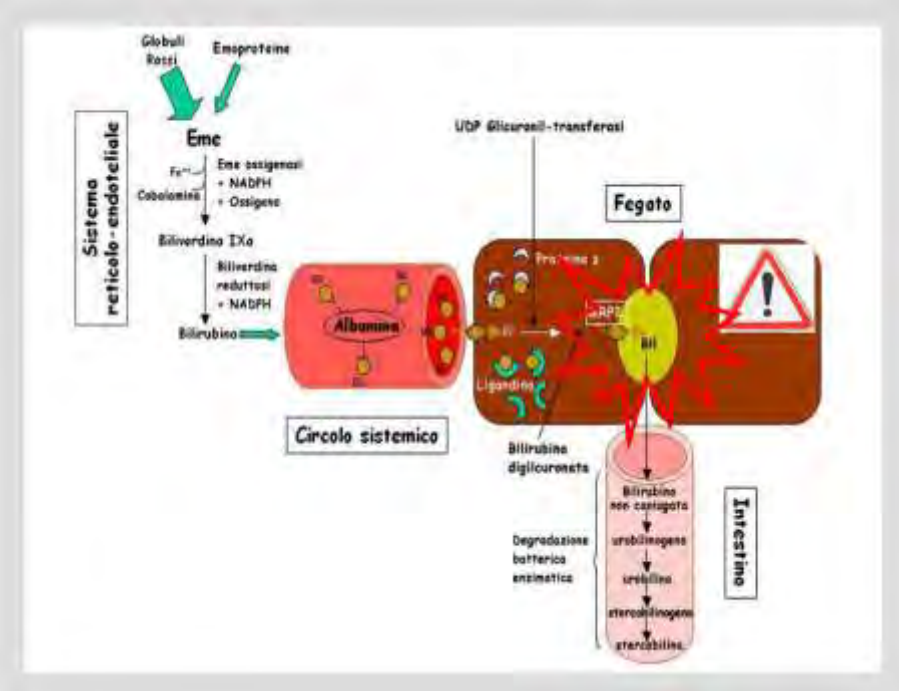
Aumento dell' effetto farmacologico

Aumento della tossicità

Ittero

Frequente nei neonati

Colorazione giallastra della pelle e della sclera causata dall'eccesso di bilirubina in circolo



Farmaci contenenti **parabeni** possono portare ad iperbilirubinemia

BEE

Immatura nel neonato

Farmaci liposolubili entrano facilmente nel SNC

Es. Fenobarbital [11]

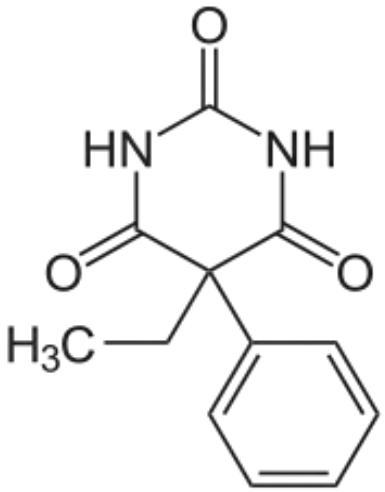


TABLE 4. Stability of Active Pharmaceutical Ingredient in SyrSpend SF.

ACTIVE PHARMACEUTICAL INGREDIENT	VEHICLE	STORAGE	MINIMUM STABILITY (DAYS)	% RECOVERY FINAL
Amiodarone hydrochloride	SyrSpend SF PH4 Cherry flavored	Room temperature	91	99.14 ± 1.73
Amiodarone hydrochloride	SyrSpend SF PH4 Cherry flavored	2°C to 8°C	91	97.91 ± 1.83
Furosemide	SyrSpend SF Alka	2°C to 8°C	14	96.40 ± 2.91
Hydrocortisone hemisuccinate	SyrSpend SF PH4	Room temperature	60	102.36 ± 1.55
Hydrocortisone hemisuccinate	SyrSpend SF PH4	2°C to 8°C	60	101.76 ± 2.63
Hydrocortisone sodium phosphate	SyrSpend SF PH4	Room temperature	60	101.23 ± 0.58
Hydrocortisone sodium phosphate	SyrSpend SF PH4	2°C to 8°C	60	102.28 ± 0.50
Nifedipine	SyrSpend SF PH4 Cherry flavored	Room temperature	92	94.03 ± 1.97
Nifedipine	SyrSpend SF PH4 Cherry flavored	2°C to 8°C	92	90.83 ± 4.30
Phenobarbital	SyrSpend SF PH4	Room temperature	154	103.61 ± 2.51
Phenobarbital	SyrSpend SF PH4 Cherry flavored	Room temperature	154	107.54 ± 1.53
Prednisolone sodium phosphate	SyrSpend SF PH4	Room temperature	30	97.58 ± 0.66
Prednisolone sodium phosphate	SyrSpend SF PH4	2°C to 8°C	30	98.47 ± 1.54
Prednisolone sodium phosphate	SyrSpend SF PH4 Cherry flavored	Room temperature	30	96.85 ± 0.77
Prednisolone sodium phosphate	SyrSpend SF PH4 Cherry flavored	2°C to 8°C	30	97.83 ± 0.70
Ranitidine hydrochloride	SyrSpend SF PH4	Room temperature	36	96.63 ± 0.70
Ranitidine hydrochloride	SyrSpend SF PH4	2°C to 8°C	58	99.31 ± 1.01
Simvastatin	SyrSpend SF PH4	2°C to 8°C	90	104.82 ± 1.68
Spironolactone	SyrSpend SF PH4	Room temperature	90	99.86 ± 1.23
Spironolactone	SyrSpend SF PH4 Cherry flavored	Room temperature	90	101.63 ± 1.81

Metabolismo

- <u>Flusso sanguigno epatico</u>

  Ridotto

  Aumenta all’ aumentare della gittata cardiaca

- Fegato

Durante crescita dimensione e volume del fegato diminuiscono in rapporto con l' aumento di peso corporeo [12]

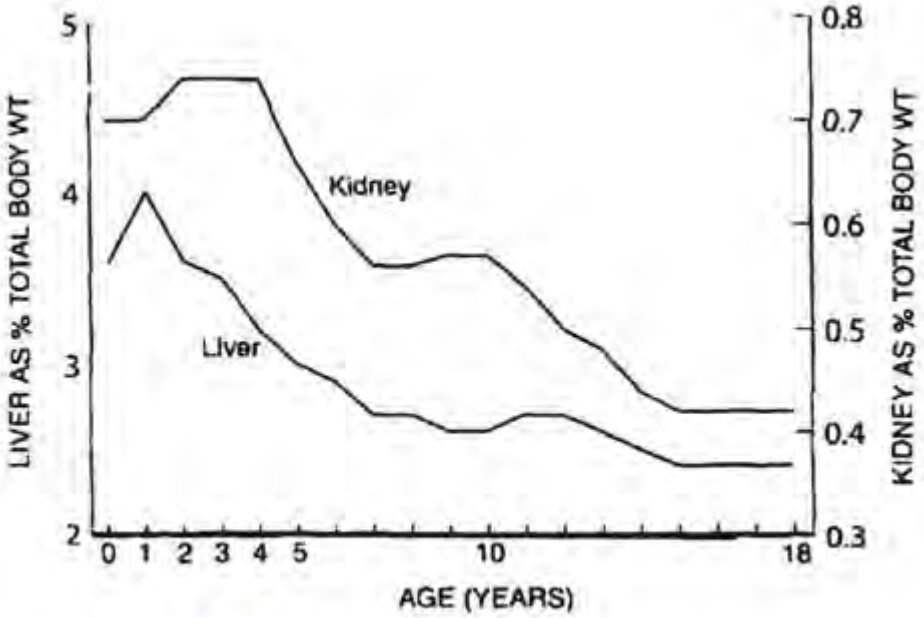


Fig. 2.6 Change in relative liver and kidney mass expressed as percentage of body weight from infancy to young adulthood [26]

Enzimi Epatici

Immaturi alla nascita

Variabilità:

- Individuale
- Di sviluppo nelle diverse fasce di età in pediatria

Fase I e Fase II

	FASE I	FASE II
Tipo di reazione	Idrolisi Ossidazione Riduzione Metilazione	Coniugazione
Aumento di idrofilia	Piccolo	Grande
Meccanismo generale	Esposizione di gruppi funzionali	Addizione di un composto polare ad un gruppo funzionale
Conseguenze	Può portare all'attivazione metabolica	Facilita l'escrezione

Sviluppo degli Enzimi di Fase I

Principale esponente è la famiglia del CYP450 (polimorfismo genetico)

Le isoforme di CYP450 sono espresse in quantità e tipologie dipendenti dall' età [13]

Attività è il 50-70% del valore nell' adulto

Principali CYP

Enzima	Neonato	Infante	Bambino	Adolescente	Implicazioni FC
CYP3A4	Ridotto 30-40% dell' adulto	Valore Adulto dal 6 mese	Aumento (1-4 anni) In ↓	Valore Adulto	↑metabolismo del Midazolam nei primi 3 mesi [18]
CYP2C9	Ridotto	Valore Adulto tra 1-6 mese	Picco (3-10 anni) In ↓	Valore Adulto	↑emivita Fenitoina (75h nei pretermine, 20h nella I settimana, 8h nella II) [17]
CYP2C19	Ridotto	Valore Adulto entro il 6 mese	Picco (3-4 anni) In ↓	Valore Adulto	↑emivita Diazepam
CYP1A2	Assente	Compare al 3 mese di vita Valori adulti al 4 mese Picco al 6 mese	Valori mantenuti	↓ al Valore Adulto Differenza di genere [16]	↑demetilazione della Caffeina e della Teofillina [15]
CYP2D6	Ridotto 20% dell' adulto	Ridotto	Valore Adulto (3-5 anni)	Valore Adulto	↓demetilazione da Codeina a Morfina ↓ controllo del dolore

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FORMULA NUMBER: 1549

FORMULA NAME: Midazolam Hydrochloride 2-mg/mL Oral Solution

DOSAGE FORM: Solution

FORMULA (Rx):

Ingredients	For: 100 mL	Lot#	RPh Initials
Midazolam Hydrochloride	200 mg	_____	_____
Stevioside (Stevia)	Powder 300 mg	_____	_____
Sorbitol Solution 70% Solution	10 mL	_____	_____
Glycerin	10 mL	_____	_____
Sodium Benzoate	200 mg	_____	_____
Flavor	qs	_____	_____
Hydrochloric Acid, Diluted (10% or 0.1N)	qs	_____	_____
Sodium Hydroxide 10% Aqueous Solution	qs	_____	_____
Water, Purified USP	qs 100 mL	_____	_____

SYNONYMS:
Versed

USE/TYPE:
Human Use
Non-Sterile Preparation

CATEGORY:
Anxiolytic Benzodiazepine
Hypnotic Sedative Non-Barbiturate

NOTES:
Midazolam hydrochloride, 20-mL of 5-mg/mL Injection is used for this formula. Additional vehicles may be used for this preparation: cherry syrup, strawberry syrup and chocolate syrup. As the drug is most stable at pH 3.6, the pH should be considered when planning for formulation. One goal in vehicle choice is to attempt to mask the bitter taste of midazolam. The strength may be varied according to the choice of the clinician. For variations of this formula, See: Formulations #1141 and #1279.

SPECIALIZED EQUIPMENT:
pH Meter
Pipette or Micro pipette

METHOD OF PREPARATION:

1. Calculate the required quantity of each ingredient for the total amount to be prepared.

2. Accurately weigh and/or measure each ingredient.

3. Add the midazolam injection to sorbitol 70% solution and 70-mL purified water.

4. Mix the stevia powder with glycerin to make a paste.

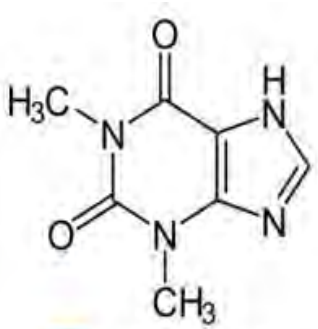
…ancora CYP

Different half-lives (hours) between neonates, infants, children and adults.

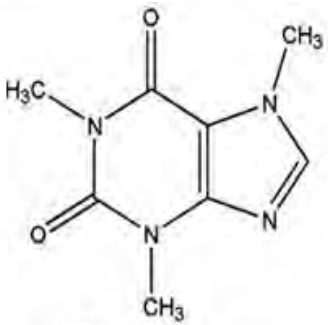
Isoenzyme	Drug	Neonate	Infant	Children	Adult
CYP1A2	Caffeine	95	7	3	4
	Theophylline	24-36			3-9
CYP 2C9	Phenytoin	30-60	2-7	2-20	20-30
CYP2C19	Phenobarbital	70-500	20-70	20-80	60-160
	Diazepam	22-46	10-12	15-21	24-48
CYP3A	Carbamazepine	8-28	–	14-19	16-36
	Lidocaine	2,9-3,3	–	1-5	1-2,2

Teofillina e Caffeina

Farmaci xantinici per il trattamento delle apnee notturne nei bambini pretermine



TEOFILLINA



CAFFEINA

Caffeine Citrate 10 mg/mL Oral Liquid

Loyd V. Allen, Jr., PhD
Professor Emeritus
College of Pharmacy, University of Oklahoma
Oklahoma City, Oklahoma

US Pharm. 2013;38(4):36-37.

FORMULA

Caffeine Citrate 10 mg/mL Oral Liquid

Rx (for 100 mL):	Ingredient		
	Caffeine citrate		1 g
	Potassium sorbate		100 mg
	Sodium citrate		1 g
	Sorbitol		20 g (optional)
	Purified water	qs	100 mL

Method of Preparation: Calculate the required quantity of each ingredient for the total amount to be prepared. Accurately weigh or measure each ingredient. Dissolve the caffeine citrate, potassium sorbate, sodium citrate, and sorbitol (if used) in about 90 mL of Sterile Water for Injection. Add sufficient Sterile Water for Injection to volume and mix well. Filter through a sterilizing filter into sterile containers; package and label.

Use: Caffeine has been used as a respiratory stimulant in neonates.

Packaging: Package this preparation in sterile, tight, light-resistant containers.[1]

Labeling: Keep out of reach of children. Use only as directed.

Stability: If this preparation is sterility tested, a beyond-use date of up to 6 months at either room temperature or refrigerated temperature may be used.[1,2]

Quality Control: Quality-control assessment can include weight/volume, pH, specific gravity, active drug assay, sterility, color, rheologic properties/pourability, physical observation, and physical stability (discoloration, foreign materials, gas formation, mold growth).[3]

… e poi CYP

Table 3. Isoenzyme activity in pediatric population compared to adults and examples.

Isoenzyme	Pediatric population activity	Drug class	Examples
CYP1A2	↓ until 2 years	Antidepressant Bronchodilator Diuretic	Duloxetine Theophylline Triamterene
CYP2C9	↓ until 1-2 years	Anticoagulant Antidepressant Nonesteroidal antiinflammatory	Warfarin Phenytoin Diclofenac,ibuprofen, naproxen, tolbutamide
CYP2C19	↓ until 10 years	Antidepressant Benzodiazepine Proton pump inhibitor	Citalopram, sertraline Diazepam Lansoprazole, omeprazole, pantoprazole
CYP2D6	↓ until 12 years	Analgesic Antidepressant Antihistamine Antipsychotic ß-Blocker	Codeine, tramadol amitriptyline, desipramine, doxepin, imipramine, fluoxetine, nortriptyline, paroxetine, venlafaxine Diphenhydramine Risperidone Labetalol, metoprolol
CYP3A4	↓ until 2 years	Analgesic Antiepileptic Antifungal Antihistamine Antiretroviral Benzodiazepine	Alfentanil, fentanyl Carbamazepine Itraconazole, ketoconazole loratadine Indinavir, lopinavir ritonavir, saquinavir Alprazolam, midazolam
MAO A	↑ until 2 years		
MAO B	≈		
N-Methyltransferases	≈		
UGTs	↓ until 7-10 years	Analgesic Antiepileptic Benzodiazepine	Morphine Lamotrigine Clonazepam, lorazepam
NAT2	↓ until 1-4 years	Antihypertensive Antiinfectious	Hydralazine Isoniazid

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FORMULA NUMBER: 896

FORMULA NAME: Isoniazid 10-mg/mL in Sorbitol Solution, Preserved, Human, Veterinary

DOSAGE FORM: Solution

FORMULA (Rx):

Ingredients	For: 100 mL	Lot#	RPh Initials
Isoniazid	1 g		
Sorbitol Solution 70% Solution	50 mL		
Methylparaben	200 mg		
Propylparaben	20 mg		
Water, Purified USP	qs 100 mL		

SYNONYMS:
INH Solution; Nydrazid

USE/TYPE:
Human Use
Veterinary Use
Non-Sterile Preparation

CATEGORY:
Anti Mycobacterial
Anti Protozoal
Anti Tubercular

NOTES:
Prepare with dispatch and in subdued light. Review Who Health Organization (WHO) for Global Tuberculosis Reports, current as of formula date: Report 2016.

SPECIALIZED EQUIPMENT:
Vortex or Magnetic Stirrer High-Shear

METHOD OF PREPARATION:

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Dissolve the methylparaben and propylparaben in about 45-mL of heated purified water.
4. After the solution cools, add the isoniazid and sorbitol solution.
5. Add sufficient purified water to volume and mix well.
6. Package and label.

LABELING:
For Oral Use Only
Keep Out of Reach of Children

For Veterinary Use
Shake Well - Keep in Refrigerator

CYP3A7 [14]

Isoforma predominante nel neonato

Già durante il periodo fetale

Picco alla nascita, poi diminuisce rapidamente ai valori adulti

CYP1A2

Bambini > 4 mesi valori simili all' adulto

Aumento dal 6 mese oltre ai valori dell' adulto fino alla pubertà

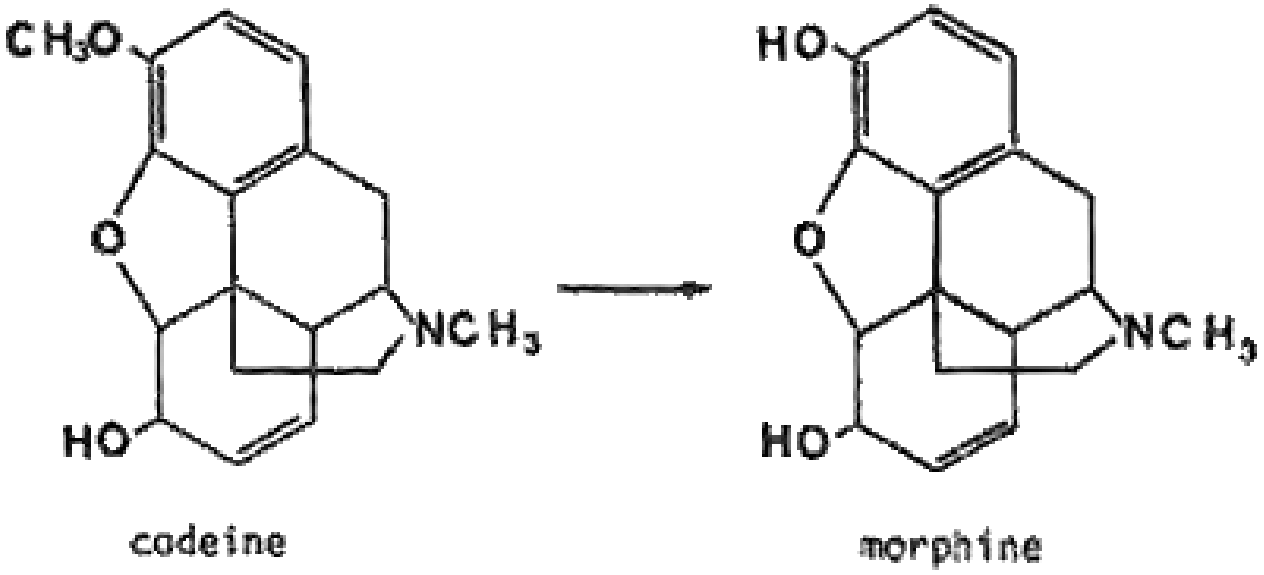
Differenza nell' ontogenesi di questo enzima su base sessuale. La velocità di demetilazione diminuisce:

- ragazze al secondo stadio della scala di Tanner
- ragazzi al 3-4 stadio [19]

CYP2D6

20% del valore dell' adulto

Minor controllo del dolore nel bambino



Sviluppo degli Enzimi di Fase II

Enzima	Neonato	Infante	Bambino	Adolescente	Implicazioni FC
N-Acetil Transferasi-2	Ridotto	Ridotto	Valore Adulto tra 1-3 anni	Valore Adulto	↓acilazione della Sulfapiridina e ↑ degli effetti collaterali
Sulfo-Transferasi	Quasi completamente sviluppata	Attività in crescita	Valore Adulto	Valore Adulto	---
Glucuronil Transferasi	Ridotto	Valore Adulto tra 3-6 mesi	Valore Adulto	Valore Adulto	Tossicità da CAF nel neonato

Inoltre…

- Metabolismo epatico ↑ nei neonati < 10 giorni di vita. Probabilmente è dovuto alle dimensioni del fegato rispetto al resto del corpo

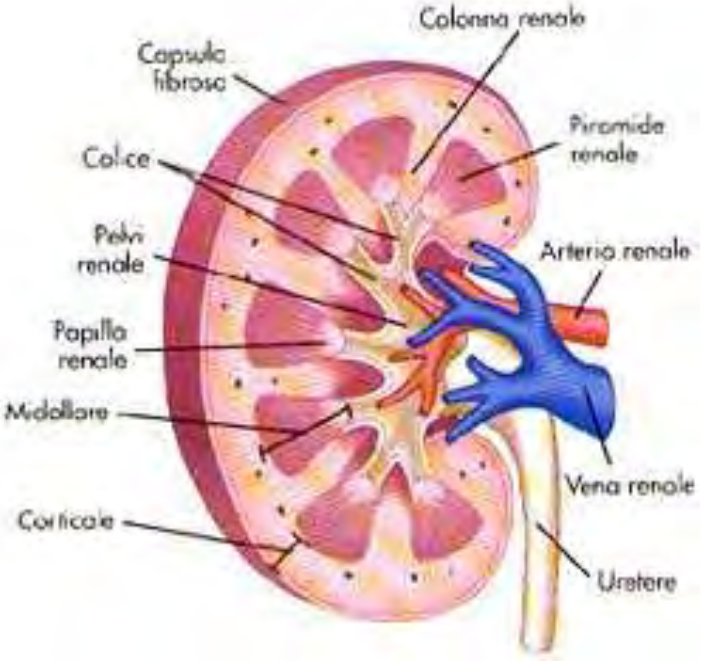
- Attenzione ai farmaci che assume la madre in allattamento → Induzione enzimatica

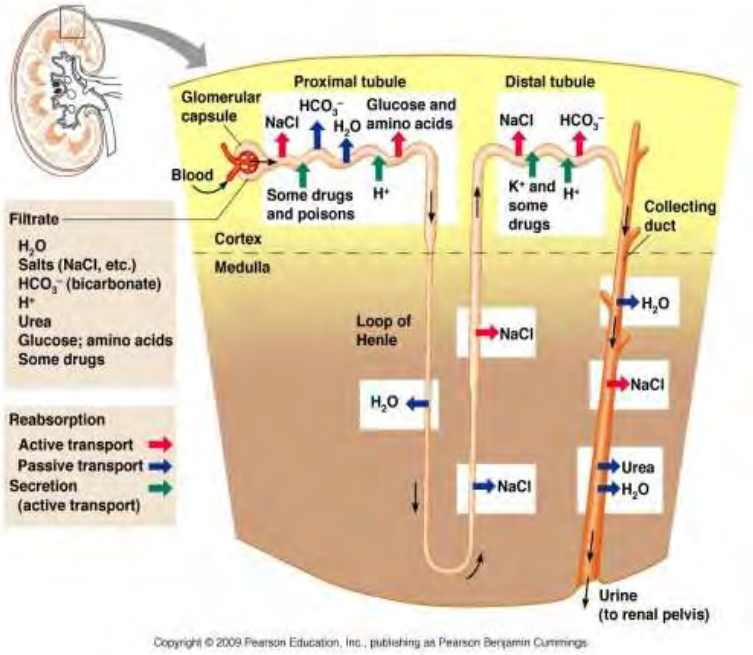
Meccanismi di escrezione

Eliminazione

Ridotta per:

- Basso grado di perfusione renale
- Sviluppo incompleto dell' organo





Filtrazione Glomerulare

Entro 7 giorni: 50%

8-12 mesi: valore dell' adulto [21]

1-2 anni vede un GFR più alto di quello adulto [22] [23]

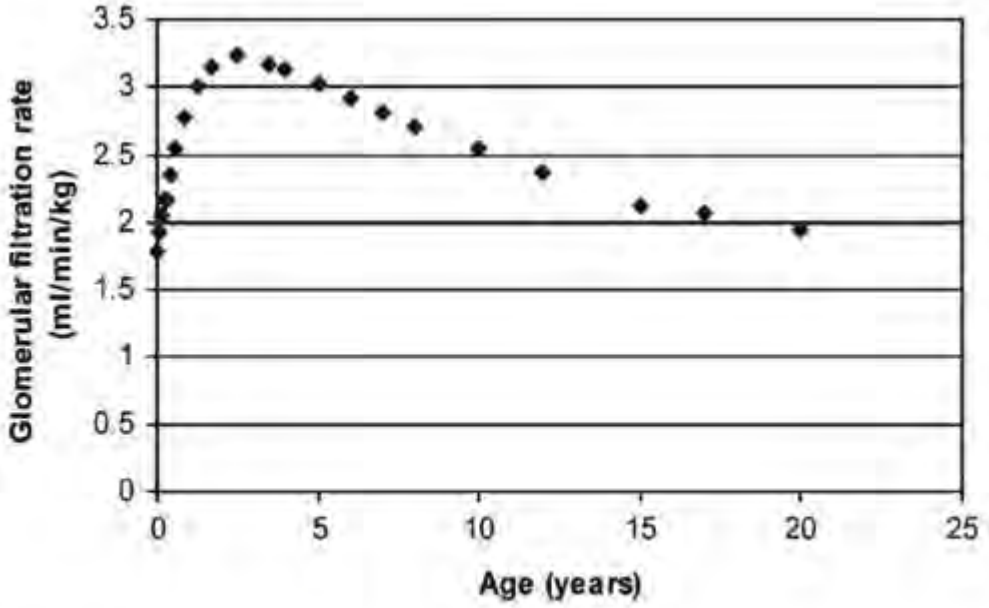
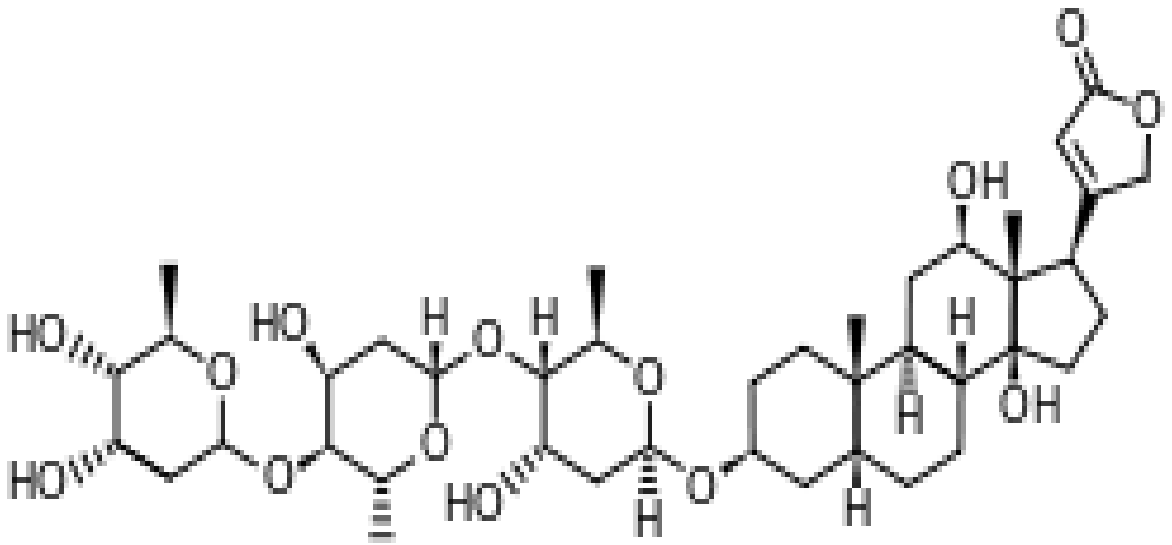


Fig. 2.7 Human GFR vs. age [8]

Digossina

↑ Dose per Kg per avere l' effetto terapeutico

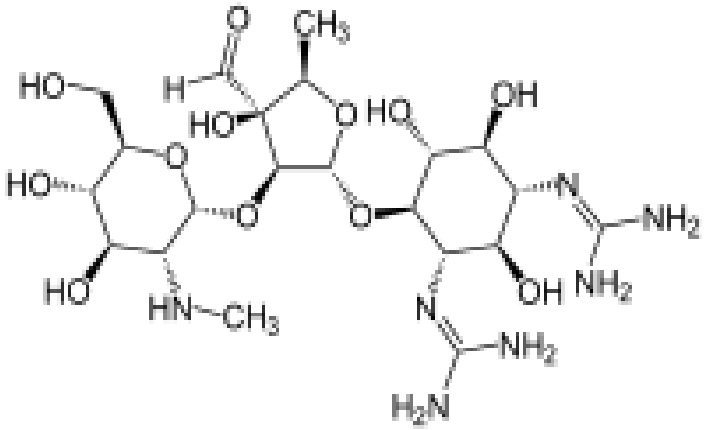


Secrezione Tubulare

Neonato: 20% del valore dell' adulto

6-7 mese: valori dell' adulto

Es. Aminoglicosidi-Streptomicina



Sperimentazione Clinica in Pediatria

La maggior parte dei farmaci sul mercato sono spesso privi dell'autorizzazione per l'uso pediatrico

E scarse sono le sperimentazioni cliniche pediatriche

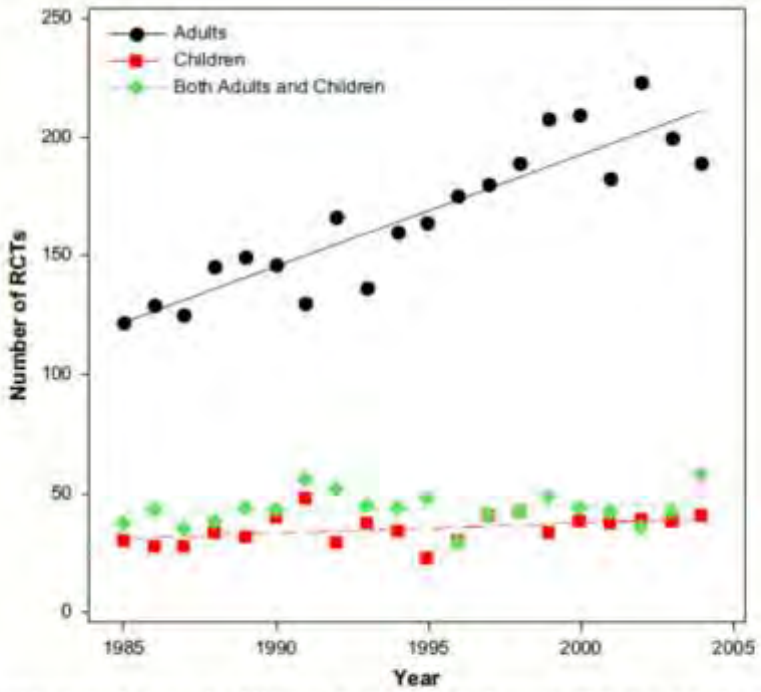


Fig.4. Il grafico mostra il numero di pubblicazioni di studi clinici randomizzati (RCT), divisi per età, nelle cinque principali riviste scientifiche internazionali di ambito medico, nel periodo 1985-2004 (Fonte: Cohen E., 2007).

Motivazioni [26]

- Economiche

- Pratiche
  - ridotto numero di pazienti pediatrici per numerose patologie
  - la necessità di studiare bambini di diverse fasce di età;
  - la necessità di preparare formulazioni dei farmaci appropriate per i bambini
  - la difficoltà di reclutare i pazienti

Motivazioni

- Etiche: consenso è necessario per autorizzare la ricerca → bambini non sono in grado di valutare autonomamente le implicazioni

Off Label

Farmaci dati fuori dall' indicazione terapeutica

Dal 13% al 60% delle prescrizioni pediatriche

[27]

Table 1 Off-label categories

Off-label category	Description
Age	Drug not recommended in the SmPC below a certain age
Weight	Drug not recommended in the SmPC for children below a certain weight
Absence of pediatric information	No mention at all in the SmPC regarding pediatric use
Lack of pediatric clinical data	Stated lack of evidence of efficacy and safety in pediatric patients in the SmPC
Contraindication	Statement in the SmPC that the drug is contraindicated in children
Indication	Drug prescribed for indications outside of those listed in the SmPC
Route of administration	Drug administered by a route not described in the SmPC

SmPC, Summary of Product Characteristics.

Leggi per Off Label in Italia

1. Legge 94 del 1998-Art. 3

“In singoli casi il medico puo', sotto la sua diretta responsabilita' e previa informazione del paziente e acquisizione del consenso dello stesso, impiegare un medicinale prodotto industrialmente per un'indicazione o una via di somministrazione o una modalita' di somministrazione o di utilizzazione diversa da quella autorizzata, ovvero riconosciuta agli effetti dell'applicazione dell'articolo 1, comma 4, del decreto-legge 21 ottobre 1996, n. 536, convertito dalla legge 23 dicembre 1996, n. 648, qualora il medico stesso ritenga, in base a dati documentabili, che il paziente non possa essere utilmente trattato con medicinali per i quali sia gia' approvata quella indicazione terapeutica o quella via o modalita' di somministrazione e purche' tale impiego sia noto e conforme a lavori apparsi su pubblicazioni scientifiche accreditate in campo internazionale.”

Leggi per Off Label in Italia

2. Legge 648 del 1996-Art.1

"Qualora non esista valida alternativa terapeutica, sono erogabili a totale carico del Servizio sanitario nazionale, a partire dal 1 gennaio 1997, i medicinali innovativi la cui commercializzazione e' autorizzata in altri Stati ma non sul territorio nazionale, i medicinali non ancora autorizzati ma sottoposti a sperimentazione clinica e i medicinali da impiegare per un'indicazione terapeutica diversa da quella autorizzata, inseriti in apposito elenco predisposto e periodicamente aggiornato dalla Commissione unica del farmaco conformemente alle procedure ed ai criteri adottati dalla stessa. L'onere derivante dal presente comma, quantificato in lire 30 miliardi per anno, resta a carico del Servizio sanitario nazionale nell'ambito del tetto di spesa programmato per l'assistenza farmaceutica."

Leggi per Off Label in Italia

3. D.Lvo 08/05/2003

Uso di farmaci non ancora completamente studiati quando le probabilità rischio/beneficio appaiano favorevoli.

A garanzia dei pazienti, la legge ne esige il consenso informato e prevede che il medicinale debba essere in fase avanzata di sperimentazione.

Farmaci sottoposti a sperimentazione nel territorio italiano o in un Paese estero, privi dell'autorizzazione all'immissione in commercio rilasciata dal Ministero della Salute possono essere richiesti direttamente all'impresa produttrice per un uso al di fuori della sperimentazione clinica e che la stessa impresa li debba fornire a titolo gratuito

Il galenico magistrale

Legge 94/98 art. 5

Prescrizione di preparazioni magistrali

1. Fatto salvo il disposto del comma 2, i medici possono prescrivere preparazioni magistrali esclusivamente a base di principi attivi descritti nelle farmacopee dei Paesi dell'Unione europea o contenuti in medicinali prodotti industrialmente di cui e' autorizzato il commercio in Italia o in altro Paese dell'Unione europea. *La prescrizione di preparazioni magistrali per uso orale puo' includere principi attivi diversi da quelli previsti dal primo periodo del presente comma, qualora questi siano contenuti in prodotti non farmaceutici per uso orale, regolarmente in commercio nei Paesi dell'Unione europea; parimenti, la prescrizione di preparazioni magistrali per uso esterno puo' includere principi attivi diversi da quelli previsti dal primo periodo del presente comma, qualora questi siano contenuti in prodotti cosmetici regolarmente in commercio in detti Paesi. Sono fatti in ogni caso salvi i divieti e le limitazioni stabiliti dal Ministero della sanita' per esigenze di tutela della salute pubblica.*

2. E' consentita la prescrizione di preparazioni magistrali a base di principi attivi gia' contenuti in specialita' medicinali la cui autorizzazione all'immissione in commercio sia stata revocata o non confermata per motivi non attinenti ai rischi di impiego del principio attivo.

3. Il medico deve ottenere il consenso del paziente al trattamento medico e specificare nella ricetta le esigenze particolari che giustificano il ricorso alla prescrizione estemporanea. Nella ricetta il medico dovra' trascrivere, senza riportare le generalita' del paziente, un riferimento numerico o alfanumerico di collegamento a dati d'archivio in proprio possesso che consenta, in caso di richiesta da parte dell'autorita' sanitaria, di risalire all'identita' del paziente trattato.

4. Le ricette di cui al comma 3, in originale o in copia, sono trasmesse mensilmente dal farmacista all'azienda unita' sanitaria locale o all'azienda ospedaliera, che le inoltrano al Ministero della sanita' per le opportune verifiche, anche ai fini dell'eventuale applicazione dell'articolo 25, comma 8, del decreto legislativo 29 maggio 1991, n. 178.

5. Le disposizioni dei commi 3 e 4 non si applicano quando il medicinale e' prescritto per indicazioni terapeutiche corrispondenti a quelle dei medicinali industriali autorizzati a base dello stesso principio attivo.

6. La violazione, da parte del medico o del farmacista, delle disposizioni del presente articolo *e' oggetto di procedimento disciplinare* ai sensi del decreto legislativo del Capo provvisorio dello Stato 13 settembre 1946, n. 233.

Dove finisce l’off label e dove inizia il magistrale, parliamone…

Alcuni esempi:

Budesonide viscosa
Idebenone cps
Glicopirrolato soluzione orale
…

Rx BUDESONIDE ORAL VISCOUS GEL 2 MG/8 ML

For 240 mL (1-month supply)

Budesonide		0.06 g
Xanthan gum		4.8 g
Saccharin sodium		0.18 g
Stevia		0.18 g
Sodium benzoate		0.45 g
Glycerin		23.6 mL
Edetate disodium		0.24 g
Flavor	qs	
Purified water	qs	240 mL

METHOD OF PREPERATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Triturate, thoroughly, in a mortar and pestle all the powders except the xanthan gum.
4. Add the glycerin gradually with constant stirring to prepare an homogenous mixture.
5. Pour the mixture into an appropriate graduate.
6. Add the purified water and flavor to 234 mL.
7. Spread the xanthan gum on top of the graduate ***without mixing*** and add purified water to final volume.
8. Pour the mixture from step 7 into an electronic mortar and pestle 500-mL jar.
9. Select the "suspension>2%" program and allow the machine to finish the preparation.
10. Fill four 60-mL amber syringes with the gel and cap it.
11. Package and label

PACKAGING

Package in capped 60-mL amber syringes.

LABELING

Keep out reach of children. Refrain eating and/or drinking 1 hour after using the medicine. For oral use. Use only as directed.

STABILITY

A beyond-use date of up to 30 days can be used for this preparation.

USE

Swallow 8 mL of the gel before bed time. Refrain eating and/or drinking 1 hour after using the medicine.

BURLO
S.C. Farmacia

Foglio di allestimento
Titolo della preparazione

Glicopirrolato 0,5mg/mL soluzione acquosa

Forma farmaceutica: ***soluzione acquosa***

COMPOSIZIONE QUALI-QUANTITATIVA

Lotto standard ***ml 100***

sodio fosfato bibasico anidro RPH	g	***0,09***
SACCAROSIO SEMOLATO FU	g	***10***
GLICOPIRROLATO	g	***0,05***
sodio fosfato monobasico anidro	g	***1,3***
acqua sterile	*q.b. a ml*	***100***
nipagina sodica	g	***0,05***

MODALITÀ DI ALLESTIMENTO

Allestire il tampone fosfato: pesare il sodio fosfato bibasico e il sodio fosfato monobasico e solbilizzarli in acqua in una beuta, riscaldando leggermente. Successivamente, pesare e solubilizzare la nipagina ed il saccarosio nella soluzione appena ottenuta ed eventualmente filtrare con garza sterile. Pesare il glicopirrolato e solubilizzarlo a freddo nella soluzione appena filtrata e portare a volume in cilindro graduato fino a 100 mL con acqua. Mescolare la soluzione ottenuta e misurarne il pH, che deve risultare ca 5,6 (pH<6). Ripartire nei contenitori finali.

Approccio ad una formulzione pediatrica

- ✓ Secundum Artem (e.g., gocce, sospensioni, sciroppi, soluzioni…)
- ✓ Allestimento estemporaneo partendo da prodotti in commercio
- × Allestimento estemporaneo utilizzando il cibo (quando?????)

Formulazioni pediatriche attualmente non disponibili

Table. Examples of medications not available in a suitable dosage form (eg, a liquid formulation) for infants and young children.

Acetazolamide
Albendazole
Amiodarone
Amitriptyline
Arginine
Aspartate
Biotin
Bupropion
Busulfan
Captopril
Carbenicillin
Cholestyramine/ Aquaphor
Clindamycin
Clobazam
Clonazepam
Clonidine
Dantrolene
~~Dexamethasone~~
Enalapril
Ethambutol
Ethionamide
Famciclovir
Glutamine
Hydroxyurea
Irbesartan
Lansoprazole
Leucovorin
Lisinopril
Lomustine
Mefloquine
Methimazole
Methotrexate
Methylphenidate
Minoxidil
Neomycin
Nicardipine
Nimodipine
Ofloxacin
Olanzapine
Pancrelipase
Paromomycin
Phenobarbital
Phenoxybenzamine
Prazosin
Primidone
Probenecid
Procarbazine
Propafenone
Pyridoxine
Riboflavin
Saquinavir
Scopolamine
Sertraline
~~Sildenafil~~
Sodium benzoate
Sotalol
Spironolactone
Testosterone
Tiagabine
Topiramate
~~Ursodiol~~
Verapamil
Vigabatrin
Warfarin
Zinc sulfate

Noi siamo quello che facciamo, sempre.
L’eccellenza non è un atto ma un’abitudine.

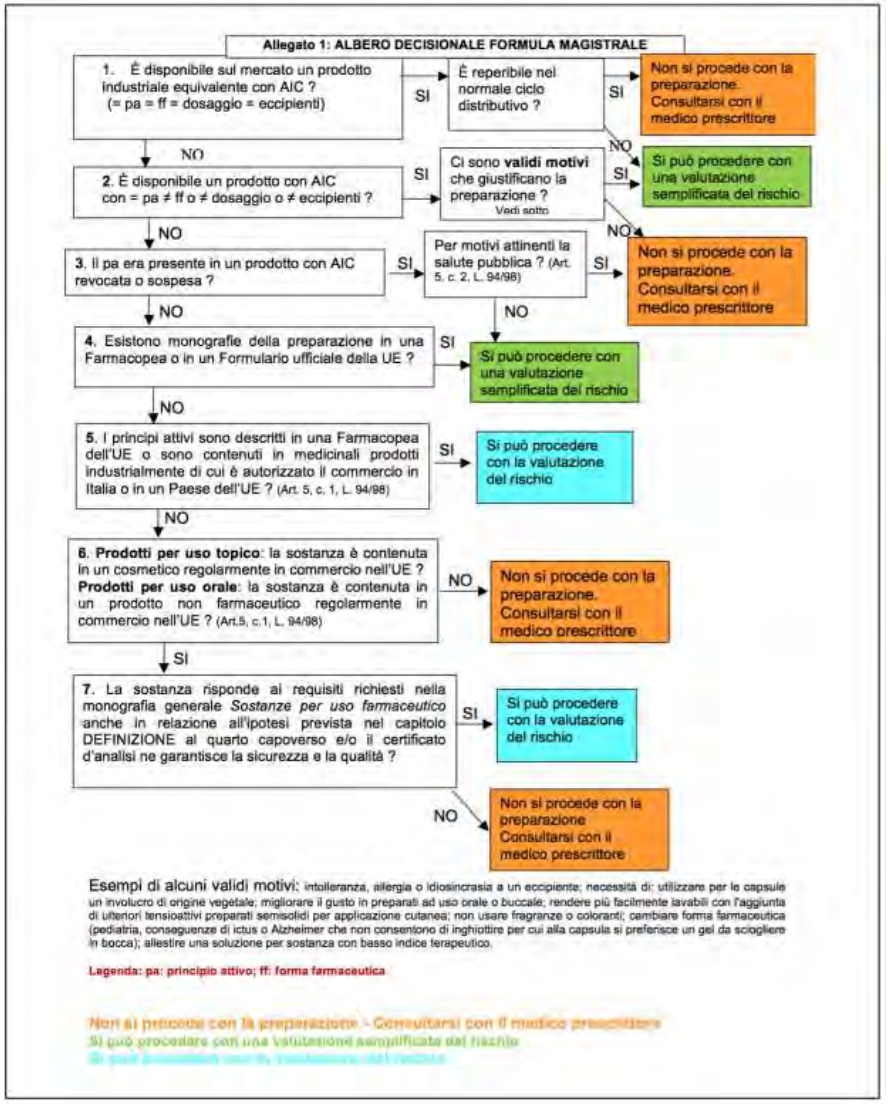
Aristotele

Formulazioni pediatriche

La valutazione del rischio

Paediatric Drug Product Design: User Instructions

Any benefit-risk evaluation of a drug product for use in any patient population is based on the assumption that the benefit is greatest and the harm is least when the drug is taken as intended. Therefore, the EMA paediatric guideline stipulates that the user instructions in the authorised product information are an integral part of the drug product design (33). Acknowl-



Da dove comincio????

Dall’ATTIVO!

Potent Medications with Potential for "Dilution Intoxication" Due to Concentration Available in Pharmaceutical Preparations

Drug	Available Concentration	Calculated Individual Dose		Dose Delivered with Flush	Delivered Dose (% Calculated)
		Volume (ml)	Amount		
Atropine	0.4 mg/ml	0.0025	0.01 mg	0.016 mg	160
Diazepam	5 mg/ml	0.05	0.1 mg	0.18 mg	180
Digoxin	100 µg/ml	0.05	5 µg	6.5 µg	130
Epinephrine	1:10,000	0.10	10 µg	11.5 µg	115
Hydralazine	20 mg/ml	0.05	1 mg	1.3 mg	130
Insulin	100 U/ml	0.001	0.1 U	0.115 U	115
Morphine	8 mg/ml	0.013	0.1 mg	0.22 mg	220
Phenytoin	50 mg/ml	0.08	4 mg	4.75 mg	120

Warfarin suspension 200mcg/ml [51]

• Warfarin sodium tablets 5mg	4
• Oraplus	50ml
• Orasweet	to 100ml

• Pack in 100ml type 1 glass bottle, with child resistant closure and 5ml oral syringe • Shelf life 7 days

• Storage room temperature

Vehicle for Oral Solution

Prepare Vehicle for Oral Solution as follows (see Pharmaceutical Compounding—Nonsterile Preparations 795).

Sucrose	80g
Glycerin	5g
Sorbitol	5g
Sodium Phosphate, Dibasic	120 mg
Citric Acid	200 mg
Potassium Sorbate	100 mg
Methylparaben	100 mg
Purified Water, a sufficient quantity to make	100 mL

Calculate the quantity of each ingredient required for the total amount to be prepared. Accurately weigh/measure each ingredient. Heat about 30 mL of Purified Water to 70 to 75 . Add the Glycerin and Methylparaben, and stir until the Methylparaben is dissolved. Add the Dibasic Sodium Phosphate, Citric Acid, Potassium Sorbate, and Sorbitol, and mix well. Add the Sucrose, and mix until dissolved; remove from the heat, and allow to cool. Add sufficient Purified Water to volume, and mix well. Adjust the pH if necessary. Package, and label.

Packaging and storage— Package in a tight, light-resistant container, and store at controlled room temperature.

Labeling— Label it to indicate that it is for use in compounding oral solutions and suspensions.

pH 791 : an apparent pH between 4.0 and 5.0.

Beyond-use date: not more than 6 months after preparation. A beyond-use date of more than 6 months may be assigned if supporting stability data exist. (See Stability Criteria and Beyond-Use Dating under Pharmaceutical Compounding—Nonsterile Preparations 795 .)

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Vehicle for Oral Suspension

Prepare Vehicle for Oral Suspension as follows (see Pharmaceutical Compounding—Nonsterile Preparations 795).

Cellulose, Microcrystalline	800 mg
Xanthan Gum	200 mg
Carrageenan	150 mg
Carboxymethylcellulose Sodium (High Viscosity)	25 mg
Citric Acid	250 mg
Sodium Phosphate, Dibasic	120 mg
Simethicone	0.1 mL
Potassium Sorbate	100 mg
Methylparaben	100 mg
Purified water, a sufficient quantity to make	100 mL

Calculate the quantity of each ingredient required for the total amount to be prepared. Accurately weigh/measure each ingredient. Heat about 90 mL of the Purified Water to 70 to 75 . Dissolve the Methylparaben, followed by the Citric Acid, Dibasic Sodium Phosphate, and Potassium Sorbate in the heated water. Remove from the heat. Constantly mixing, slowly sprinkle on the Microcrystalline Cellulose, Xanthan Gum, Carrageenan, and Carboxymethylcellulose Sodium. Continue to stir until fully hydrated, add the Simethicone, and mix well. Add sufficient Purified Water to volume, and mix well. Adjust the pH if necessary. Package, and label.

Packaging and storage— Package in a tight, light-resistant container, and store at controlled room temperature.

Labeling— Label it to indicate that it is for use in compounding oral solutions and suspensions.

pH 791 : an apparent pH between 4.0 and 5.0.

Beyond-use date— See Beyond-use date under Vehicle for Oral Solution, Sugar Free.

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

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Pediatric Excipients

Fig. 1. Volume and size indication of 250 mg oral powder, 2-mm tablet, several 2-mm tablets and 4-mm tablet on plastic spoon for infant use

La scelta

- **B. Potential Excipients Intended for Short-Term Use**

- use in products that are limited by labeling to clinical use of 14 or fewer consecutive days per treatment

- **C. Potential Excipients Intended for Intermediate Use**

- more than 2 weeks but less than or equal to 3 months per treatment

- **D. Potential Excipients Intended for Long-Term Use**

- more than 3 months in a given patient (either as a single treatment episode or as a result of multiple courses of therapy to treat a chronic or recurrent condition) include at least the following:

Oral Formulations for Children
– The Down Side –

- Solutions often contain potentially toxic excipients
- Suspensions often result in unequal drug delivery over time due to nonuniform dispersal
- Suspensions often have palatability problems due to **both** taste and texture

Safety Considerations with Excipients

Although excipients are expected to be pharmacologically inactive, certain patients may experience a variety of adverse effects, ranging from **hypersensitivity** or **allergic reaction** associated with a **coloring agent in an oral dosage form** to intracranial hemorrhage with a **benzyl alcohol** preservative in an **IV** dosage form.

All **sweeteners** containing sucrose and fructose may affect blood sugar;

sorbitol and **xylitol** may cause osmotic diarrhea.

Lactose should be avoided in patients who are lactose intolerant.

Ethanol is a solvent minimally used in oral liquid formulations that has largely been replaced by other excipients. Ethanol can cause hypoglycaemia

Para-hydroxybenzoates can cause hypersensitivity reactions and exacerbate the symptoms of asthma. It has also been suggested that benzoates and para-hydroxybenzoates can aggravate neonatal hyperbilirubinaemia by displacing bilirubin which is bound to plasma proteins

Propylene glycol is commonly used as a solvent in oral, topical, and injectable drugs (eg, phenobarbital,phenytoin, diazepam, lorazepam). This vehicle is especially useful to solubilize drugs with limited water solubility.

l Patients aged <4 years may accumulate propyleneglycol due to decreased metabolism, and those receiving multiple drugs containing this solvent are at high risk of developing central nervous system depression and hyperosmolality. Certain extemporaneously prepared suspensions, without sufficient preservative, may pose risks associated with microbial contamination.

Pediatric Excipients

Table 3 Excipients known to be harmful and potentially harmful to neonates used in study population, their applications and safety concerns

Excipient	Functional category†	Applications and typical concentration ranges†	Safety concern
Known to be harmful to neonates			
Parabens (methyl- and propyl parahydroxybenzoate)	Antimicrobial	Antimicrobial activity against yeasts and molds. Combination of Methyparaben (0.18%) and propylparaben (0.02%) for parenteral formulations. In combinations with propylene glycol (2-5%)/ imidurea	Hyperbilirubinemia in neonates. Irritant in injections / ophthalmic drugs. Hypersensitivity reactions. [18,19]
Saccharin sodium	Sweetening	0.02-0.5% w/w*	Urticaria with pruritus and photosensitivity reactions. [14]
Sodium benzoate	Antimicrobial, tablet / capsule lubricant	0.02-0.5% in oral medicines; 0.5% in parenteral medicines; 2-5% w/w tablet lubricant	Contact urticaria. [21] Topical irritant. Increased risk of hyperbilirubinaemia in neonates.
Benzyl alcohol	Antimicrobial, solvent	Up to 2% v/v* in parenteral/oral preparations, typically 1% v/v. 5% v/v and up used as solubilisers. 10% v/v local anaesthetic properties (parenterals, ophthalmic solutions, oitments)	Headache, vertigo, nausea, vomiting, diarrhea, metabolic acidosis, seizures, gasping. Hypersensitivity; fatal toxic syndrome in premature infants. Pain on injection, [8,18-20]
Benzalkonium chloride	Antimicrobial, antiseptic, solubilising, wetting	Ophthalmic preparations – preservative, 0.01-0.02% w/v*; In combination with other preservatives	Ototoxic when applied to ear, skin irritation and hypersensitivity Bronchoconstriction in asthmatics. Eye irritation. [18-20]
Propylene glycol	Antimicrobial, humectant, plasticizer, solvent, stabilizing, water-miscible cosolvent	Humectant – topical – approx.15%. Preservative –solutions / semisolids – 15-30%. Solvent or cosolvent: aerosol solutions 10-30%, oral solutions 10-25%, parenterals 10-60%, topical 5-80%	Skin irritation. Central nervous system (CNS) depression. High doses - cardiovascular, hepatic, respiratory adverse events. [18-20]
Polysorbate 80	Dispersing, emulsifying, non-ionic surfactant, solubilising, suspending, wetting	Emulsifying: alone in oil-in-water emulsions 1-15%; in combination 1-10%. To increase water-holding prop of ointments 1-10%. Solubilising: poorly soluble API*s in lipophilic bases 1-5%; insoluble APIs in lipophilic bases 0.1-3%	E-Ferol syndrome - thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, metabolic acidosis. [18]
Ethanol	Solvent	In the USA, the max quantity of alcohol included in over the counter (OTC) medicines 0.5% v/v for products for use by children under 6 years of age. Parenteral products containing up to 50% of alcohol (e 95 or 96% v/v)	CNS depression - muscle incoordination, visual impairment. Negative synergic effects on CNS when associated with dextromethorfan. Chronic toxicity [8,18,20]

Pediatric Excipients

Potentially harmful excipients

Sodium metabisulphite	Antimicrobial, antioxidant	Antioxidant in oral, parenteral, and topical formulations: 0.01–1.0% w/v, intramuscular 27% w/v. Antimicrobial: syrups.	Hypersensitivity. Paradoxical bronchospasm, wheezing, dyspnoe and chest tightness in asthmatic children.[18-20]
Colloidal anhydrous silica	Adsorbent; anticaking; emulsion stabilizer; glidant; suspending; tablet disintegrant; thermal stabilizer; viscosity-increasing	Improves flow properties of dry powders (0.1-0.5%) (tabletting); stabilizes emulsions (1.0-5.0%); thixotropic thickening/ suspending (2.0-10.0%); in aerosols to promote particulate suspension, eliminate hard settling, minimize clogging of spray nozzles (0.5-2.0%)	A possible sarcoidosis-inducing antigen [22]
Anhydrous sodium hydrogen phosphate (monobasic, dibasic)	Buffering; emulsifying; sequestering.	Buffering agent; sequestering agent. Concentrations are dependent on the formulation.	Gastrointestinal (GI) disturbances including diarrhea, nausea, and vomiting [18]
Sodium bicarbonate	Alkalizing; therapeutic.	To produce or maintain an alkaline pH in a preparation	Exacerbation of chronic heart failure in elderly [18]
Macrogols - polyethylene glycol	Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.	High molecular weight macrogols can be used as lubricants in tablet formulations; water solubility and bad penetration through skin makes them useful as ointment bases	Hypersensitivity reactions, hyperosmolarity, metabolic acidosis, and renal failure in burn patients. [18]

Nifedipine 10-mg/mL Oral Suspension

Rx

		For 100 mL
Nifedipine		1 g
Glycerin		40 mL
Peppermint oil		qs
Polyethylene glycol 400	qs	100 mL

Note: Due to the light sensitivity of nifedipine, compounding of this preparation should be in subdued light.

METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Add the nifedipine powder to about 55 mL of polyethylene glycol 400 (PEG 400) and mix well.
4. Add the glycerin and mix well.
5. Heat the mixture to about 95°C with stirring and maintain that temperature until the drug dissolves.
6. Cool to room temperature, add the peppermint oil, and mix well.
7. Add sufficient PEG 400 to final volume and mix well.
8. Package and label.

PACKAGING

Package in tight, light-resistant containers (amber bottles).[1]

LABELING

Keep out of reach of children. Use only as directed. Shake well. Protect from light.

STABILITY

A beyond-use date of 35 days can be used for this preparation.[1,2]

USE

This preparation has been used in hypertension and angina in patients who cannot take oral solid dosage forms.

QUALITY CONTROL

Quality-control assessment can include weight/volume, pH, specific gravity, active drug assay, color, rheological properties/pourability, physical observation, and physical stability (discoloration, foreign materials, gas formation, mold growth).[3]

DISCUSSION

Nifedipine ($C_{17}H_{18}N_2O_6$, MW 346.33, Adalat, Procardia) is a 1,4-dihydropyridine-derivative calcium-channel blocking agent used in the management of Prinzmetal variant angina and chronic stable angina pectoris, hypertension, Raynaud's Phenomenon, Preterm labor, and acute myocardial infarction. It occurs as a yellow powder that is affected by exposure to light. It is practically insoluble in water and soluble in alcohol.[1,4]

Glycerin ($C_3H_8O_3$, MW 92.10, glycerol, 1,2,3-propane triol) occurs as a clear, colorless, odorless, viscous, hygroscopic liquid with a sweet taste about two thirds as sweet as that of sucrose. It is used as an antimicrobial preservative (>20% concentration), emollient and humectant (up to 30% concentration), in ophthalmic formulations (0.5% to 3% concentration), plasticizer in film coating for tablets, parenteral solvent (up to 50% concentration), and as a sweetening agent in alcoholic elixirs (up to 20% concentration). It has a specific gravity of about 1.25. It is miscible with water, methanol, and 95% ethanol; practically insoluble in oils and chloroform and slightly soluble in acetone. It is hygroscopic and should be stored in air-tight containers in a cool place. It is not prone to oxidation but will decompose on heating. When mixed with water, ethanol, and propylene glycol, the mixtures are chemically stable. Incompatibilities include strong oxidizing agents, where it may explode, such as chromium trioxide, potassium chlorate, and potassium permanganate. When mixed with zinc oxide or basic bismuth nitrate and exposed to light, it will form a black discoloration. When mixed with phenols, salicylates or tannin, a darkening of the mixtures may occur due to an iron contaminant in the glycerin. It will also form a strong acid complex, glyceroboric acid, when mixed with boric acid.[5]

Polyethylene glycol (carbowax, PEG, polyoxyethylene glycol) is an addition polymer of ethylene oxide and water. Polyethylene glycol 400 is a clear, colorless or slightly yellow-colored, viscous liquid with a slight, but characteristic odor and a bitter, slightly burning taste. The density is in the range of 1.11 to 1.14 g/mL, and the freezing point 4°C to 8°C. It is soluble in water and miscible in all ratios with other PEGs. Also, it is soluble in acetone, alcohols, glycerin, and glycols. It is chemically stable, does not support microbial growth, and does not become rancid.[6]

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5. Alvarez-Nunez FA, Medina C. Glycerin. In: Rowe RC, Sheskey PJ, Quinn ME, eds. *Handbook of Pharmaceutical Excipients*. 6th ed. Washington, DC: American Pharmaceutical Association; 2009: 283–286.
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In experimental animals single doses of PEG are practically nontoxic.

When lethal doses are administered they cause narcosis and death from respiratory paralysis. The oral toxicity decreases with increasing molecular weight. Only after very high PEG doses does long-term oral administration of those PEGs which have been studied lead to adverse effects on kidney and liver, body weights and survival. In a 13-week inhalation study, very high concentrations of PEG200 aerosols proved to be practically non-toxic.

Pediatric Excipients

Table 3 Excipients known to be harmful and potentially harmful to neonates used in study population, their applications and safety concerns *(Continued)*

Trometamol	Buffering	Buffering agent, buffer range from 7.1–9	Hypersensitivity reactions. [23]
Cetostearyl alcohol	Emollient; emulsifying; viscosity-increasing.	Increasing viscosity; stabilizes emulsions; co-emulsifier; decreasing the amount of surfactant required	Hypersensitivity reactions. Contact dermatitis. [18,19]
Sodium lauryl sulphate	Anionic surfactant; detergent; emulsifying; skin penetrant; tablet and capsule lubricant, wetting	Tablet lubricant (1.0-2.0%)	Irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. [18]
Sorbitan stearate	Dispersing; emulsifying; nonionic surfactant; solubilizing; suspending; wetting	When used alone produces water-in-oil emulsions / microemulsions. In combination with polysorbate produces water-in-oil or oil-in-water emulsions / creams.	Hypersensitive reactions.[18]
Lactic acid	Acidulant	In injections in the form of lactate as a source of bicarbonate (0.012-1.16%)	Neonates have difficulty in metabolizing R-lactic acid, and this isomer and the racemate should therefore not be used in infants aged less than 3 months old. [18]
Sodium cyclamate	Sweetening	0.17% w/v as sweeter, in combination with saccharin	Photosensitivity. [18]
Disodium edetate	Chelating	Forms stable water-soluble complexes with alkaline earth and heavy-metal ions; concentrations 0.005-0.1%	Local inflammatory reactions. [18]
Gelatin	Coating; film-forming; gelling; suspending; tablet binder; viscosity-increasing	Tablet binder; microencapsulation	Local irritation. Hypersensitivity reactions, including serious anaphylactoid reactions [21]
Povidone	Disintegrant; dissolution enhancer; suspending; tablet binder	Binder in wet-granulation process; coating; solubilizer for poorly soluble drugs (0.5-5%)	Subcutaneous granulomas at the injection site. [21]
Trolamine	Alkalizing; emulsifying	When mixed in equimolar proportions with a fatty acid an emulsifying agent to produce fine-grained, stable oil-in-water emulsions will be formed (2-4%)	Hypersensitivity, skin irritant. [18]

Pediatric Excipients

Cresol	Antimicrobial preservative; disinfectant.	Antimicrobial preservative in parenteral formulations (0.15-0.3%)	Skin hypersensitivity reactions. [18]
Maltose	Sweetening; tablet diluent	Osmotic - ophthalmic drops and parenteral inf.	Single report of hyponatremia in a liver transplantation patient. [18]
Sorbic acid	Antimicrobial	As antimicrobial preservative (0.05-0.2%)	Irritant and allergic hypersensitivity skin reactions. [18,19]
Boric acid	Antimicrobial, buffering	As antimicrobial preservative in eye drops. Good buffering capacity to control pH.	Poisoning - abdominal pain, vomiting, diarrhea, erythematous rash, CNS depression. Convulsions, hyperpyrexia, and renal tubular damage. [18]
Borax	Alkalizing; antimicrobial; buffering; disinfectant; emulsifying; stabilizing	Antimicrobial preservative in eye preparations	Vomiting, diarrhea, erythema, CNS depression, and kidney damage. [18]
Glycine	Buffering; bulking; freeze-drying; tablet disintegrant; wetting	Cofreeze-dried excipient in injectable formulations	Disturbances of fluid and electrolyte balance; cardiovascular and pulmonary disorders. [18]
Calcium chloride dihydrate	Antimicrobial, water-absorbing.	Dehydrating properties	Stomach and heart disturbances. Eye irritant, dermatitis. [18]
Leucine	Antiadherent; flavoring; lubricant	As antiadherent to improve the deagglomeration	Moderately toxic by the s/c route.[18]

Pediatric Excipients

Table 1 Excipients known to be harmful in neonates selected for the study [4, 8, 9]

Class	Excipient		Safety concerns
	E. no.	Name	
Preservatives	E-1519	Benzyl alcohol	Should not be given to neonates due to their immature metabolism: fatal toxic syndrome in premature infants
			Vomiting, diarrhea
			Metabolic acidosis
			Seizures
			Gasping
			Hypersensitivity
	E-210	Benzoic acid	May increase the risk of jaundice in neonate
		Benzoates	
	E-211	Sodium benzoate	
	E-212	Potassium benzoate	
		Parabens	Hyperbilirubinemia in neonates in injection
	E-216	Propyl p-hydroxybenzoate	Hypersensitivity reactions
	E-217	Sodium propyl p-hydroxybenzoate	
	E-218	Methyl p-hydroxybenzoate	
	E-219	Sodium methyl p-hydroxybenzoate	
		Sulfites	Hypersensitivity
	E-223	Sodium metabisulphite	Paradoxical bronchospasm, wheezing, dyspnea
	E-385	Edetate disodium (or disodium EDTA)	Hypocalcemia if used over an extended period of time or if administered too rapidly by intravenous infusion
			Local inflammatory reactions
			Should be used with caution in patients with renal or cardicac impairment
Sweeteners	–	Sucrose	Elevation of blood glucose
			Patients with hereditary fructose intolerance: contraindication
	–	Fructose	Elevation of blood glucose
			Patients with hereditary fructose intolerance: contraindication
			Laxative effects when administered orally

Pediatric Excipients

	E-420	Sorbitol	Osmotic diarrhea
			Patients with hereditary fructose intolerance: contraindication
	E-967	Xylitol	Osmotic diarrhea
	E-951	Aspartame	Harmful in patients with phenylketonuria and contraindicated in homozygous autosomal recessive patients
			Hypersensitivity
	E-954	Saccharin and its sodium, calcium and potassium salts	Hypersensitivity reactions
Fillers and solvents	–	Lactose	Patients with lactose intolerance: caution
			Diarrhea, dehydration, metabolic acidosis
	–	Ethanol	Limited metabolic pathway (alcohol dehydrogenase) in children younger than 4 years: depression of the central nervous system
	E-1520	Propylene glycol	Limited metabolic pathway (alcohol dehydrogenase) in children younger than 4 years: depression of the central nervous system
			Laxative effects when administered orally
			Nephrotoxicity
	–	Castor oil	Nausea, vomiting
			Colic, and severe purgation
Dyes	E-102	Tartrazine, FD&C[a] yellow #5	Anaphylactoid reactions: urticaria, angioedema
	E-110	Orange yellow 5, Sunset yellow FCF, FD&C[a] yellow #6	Anaphylactoid reactions: urticaria, angioedema
	E-124	New Coccine, Ponceau 4, Cochineal Red A	Anaphylactoid reactions: urticaria, angioedema
–	–	Gluten	Patients with celiac disease: contraindication
			Should not be given to neonates and infants in the first three months of life

– E number not available

[a] FD&C is a designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics

QUINDI!

Bioavailability is the fraction of a compound that is absorbed from the GI tract into the general blood circulation. While high bioavailability (i.e., close to complete absorption) of API is desired after PO administration low excipient bioavailability is favored with most of the excipient metabolized in the gut or excreted unchanged in feces.

Lipinski's RULE OF FIVE

It consists of four prerequisites that are based on the number 5 and state that poor absorption from the GI tract or permeation through biomembrane is more likely when:

1. there are more than 5H-bond donors (expressed as the sum of all OHs and NHs),
2. there are more than 10H-bond acceptors (expressed as the sum of Ns and Os),
3. the molecular weight (Mw) is over 500, and
4. the log Poctanol/water is over 5.

Biopharmaceutics Classification System (BCS)

Table 1
The limiting Rule-of-Five values for oral bioavailability as well as for transdermal, ophthalmic and pulmonary drug delivery. Modified from (Choy and Prausnitz, 2011).

Route of drug administration	Mw (Da)	Log $P_{octanol/water}$	H-bond donors	H-bond acceptors
Oral drug delivery	500	5.0	5	10
Transdermal drug delivery	335	5.0	2	5
Topical drug delivery to the eye	500	4.2	3	8
Pulmonary drug delivery	500	3.4	4	10

According to the BCS, orally administered drugs are divided into 4 classes (Table 2) based on their solubility and permeability

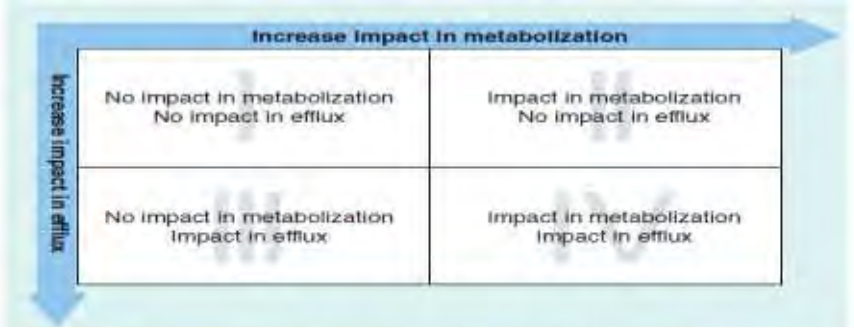
Table 2
The Biopharmaceutics Classification System is based on the aqueous drug solubility (*S*) over the pH range 1–7.5 and permeability (*P*) through GI mucosa.

Class	*S*	*P*	Characteristics
I	High	High	Water-soluble drugs (high *S* value) that are well absorbed from the GI tract (high *P* value) and in general, have the preferred physicochemical properties for optimum oral bioavailability. Primarily eliminated by metabolism
II	Low	High	Drugs that are poorly soluble in water (low *S* value) that are well absorbed from the GI tract (high *P* value) once dissolved. Primarily eliminated by metabolism
III	High	Low	Water-soluble drugs (high *S* value) that are poorly absorbed from the GI tract (low *P* value). Primarily eliminated unchanged
IV	Low	Low	Drugs that are poorly soluble in water (low *S* value) that are poorly absorbed from the GI tract (low *P* value). Primarily eliminated unchanged

BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	

BCSExcipients

BCSE class I present low risk of impact in drug safety and efficacy, and include excipients such as microcrystalline cellulose or lactose. The excipients included in this class can be replaced within technologicallyequivalent ones without major concerns.
BCSE class II and III excipients present a high risk, particularly when used with drugs that undergo intestinal metabolization or are efflux subtracts, respectively. Excipients known to belong to these classes are presented in Tables 2 and 3. These excipients should not be replaced by technologically similar ones without further studies. Any quali-quantitative change of these excipients in a formulation should consider using excipients from the same BCSE class. However, even within these ones, a large-scale bioequivalence study would be recommended in order to accommodate the inter-individual variability existent in the expression of metabolization and



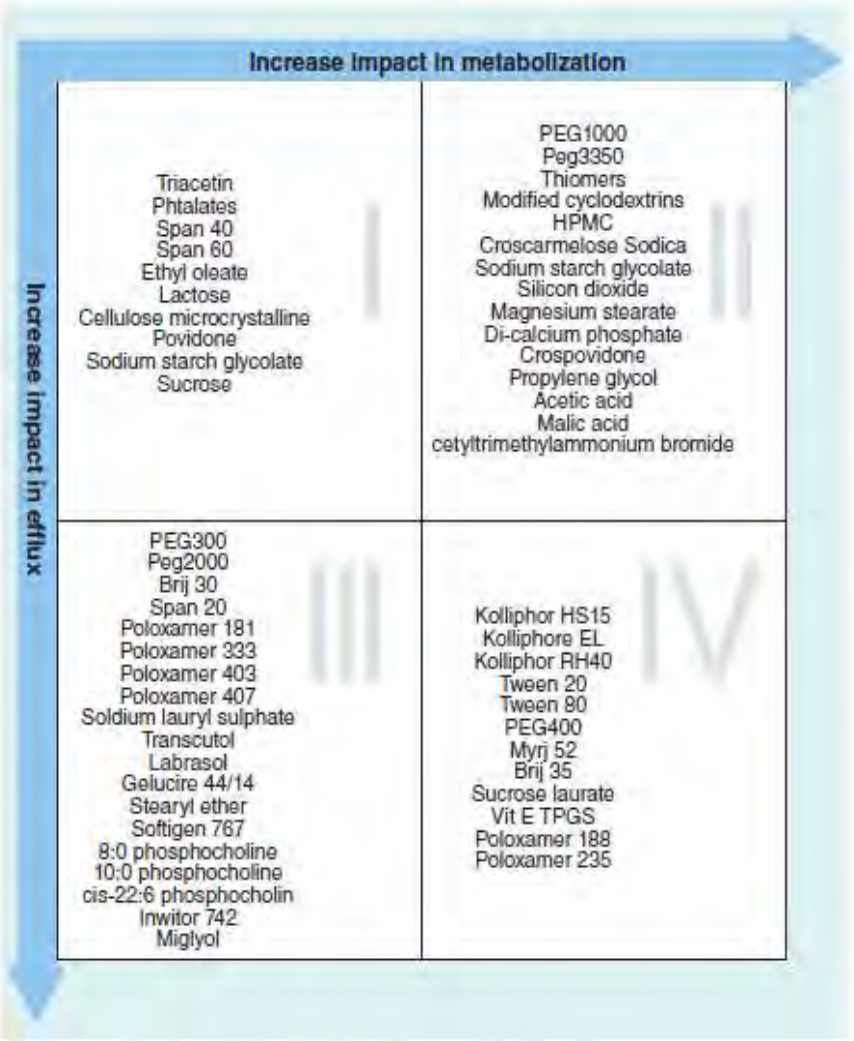


Figure 2. List of excipients included in each BCSE class.

Ad esempio…

Table 2. Excipients effect in cytochrome P450.

Excipient	CYP3A	CYP3A4	CYP3A5	CYP2C9	Glucuronidation
Kolliphor® HS15	+				+
Kolliphor® EL	+	+		+	+
Kolliphor® RH40		+		+	+
Tween-20®	+		+		+
Tween-80®	+	+	+	+	+
PEG400	+				+
PEG1000			+	+	
PEG3350	+				
Myrj® 52	±	+		+	
Brij® 35		+			
Poloxamer 188	±	+	+	+	
Poloxamer 235	+				
Poloxamer 403	–				
Poloxamer 407	–				
Vitamin E TPGS	–	+			
Thiomers		+			
Modified cyclodextrins		+		↑	
Sucrose laurate		+		+	
HPMC	+				
Croscarmelose sodium	+				
Sodium starch glycolate	+				
Silicon dioxide	+				
Magnesium stearate	+				
Dicalcium phosphate	+				
Crospovidone	+				
Propylene glycol	+				
Acetic acid	+				
Malic Acid	+				
Triacetin	↑				
Phtalates	↑				
Lactose	–				
Cellulose microcrystalline	–				
Povidone	–				
Sodium starch glycolate	–				
Sodium lauryl sulfate	–				
Sucrose	–				
Cetyltrimethylammonium bromide	+				

(+) inhibition; (–) no inhibition; (±) variable information (↑) enzymatic induction.
HPMC: Hydroxypropyl methylcellulose; TPGS: Tocopherol polyethylene glycol succinate.

Table 3. Excipients effect on transporters.

Excipient	P-gp	MRP2	BCRP	OATP
Kolliphor® HS15				+
Kolliphor® EL	+	±	+	+
Kolliphor® RH40	±	+	–	
Tween-20®	+			
Tween-80®	±	+	+	
PEG400	+	+	–	+
PEG300	+			
PEG2000		+		
Myrj® 52	+		–	
Brij® 35	+			
Brij® 30			+	
Span® 20	+		+	
Span® 40	–		–	
Span® 80	–		–	
Poloxamer 181	+			
Poloxamer 188	±	–		
Poloxamer 235	+	+	+	
Poloxamer 333	+	–		
Poloxamer 403	+			
Poloxamer 407	+	±		
Vitamin E TPGS	+	+	–	
Sodium lauryl sulfate		+		
Transcutol®		+		
Sucrose laurate	+	–		
Labrasol®	+	±		
Gelucire® 44/14	+		–	
Stearyl ether	+			
Softigen® 767	+			
8:0 phosphocholine	+			
10:0 phosphocholine	+			
cis-22:6 phosphocholin	+			
Propylene glycol	–		–	
Ethyl oleate	–		–	
Triacetin	–		–	
Inwitor 742®	+			
Miglyol®	+			

(+) inhibition; (–) no inhibition; (±) variable information.
BCRP: Breast cancer resistance protein; MRP2: Multidrug resistance associated protein 2; OATP: Organic anion transporting polypeptide; P-gp: P-glycoprotein.

Cosa può cambiare?

- Stabilità
- Biodisponibilità
- Composizione non uniforme
- Variabilità efficacia cibo-correlata

…stabilità…

CompoundingToday.com
122 N Bryant Avenue, Edmond, OK 73034 | 800.757.4572 | 405.330.0094 | info@compoundingtoday.com

FORMULA NUMBER: 1654

FORMULA NAME: Captopril 1-mg/mL Aqueous Oral Solution, Human, Veterinary

DOSAGE FORM: Solution

FORMULA (Rx):

Ingredients	For: 100 mL	Lot#	RPh Initials
Captopril	100 mg*		
Ascorbic Acid	500 mg**		
Edetate Disodium	100 mg		
Water, Purified USP	qs 100 mL		

SYNONYMS:
Capoten

USE/TYPE:
Human Use
Veterinary Use
Non-Sterile Preparation

CATEGORY:
AntiHypertensive
AntiHypertensive-ACE Inhibitor
Cardiac Agent

NOTES:
*Two x 50-mg tablets of captopril may be used, comminuted to a fine powder. **Sodium ascorbate for injection, 500mg, may be used as an alternate to ascorbic acid bulk powder USP.

SPECIALIZED EQUIPMENT:
Vortex or Magnetic Stirrer High-Shear

METHOD OF PREPARATION:

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Allow two tablets of 50-mg captopril to dissolve in 50-mL purified water in a graduate.
4. Add a 500-mg ascorbic acid tablet to the mixture and allow to dissolve.
5. Dissolve the edetate disodium in the aqueous mixture and mix well.
6. Bring to volume with purified water. Do not filter.
7. Package and label.

LABELING:
For Oral Use Only
Shake Well - Keep in Refrigerator
Keep Out of Reach of Children

PRESERVATION, PACKAGING AND STORAGE:
Tight, Light Resistant Container
Keep Refrigerated - Refrigerate Upon Receipt
Do Not Use After _____

STABILITY:
A beyond-use date of 56 days can be used for this preparation when stored in a refrigerator.

ENDOTOXIN ASSESSMENT:

USE:
Captopril is an angiotension-converting enzyme (ACE) inhibitor used to treat hypertension. The strength may be altered to meet the needs of the patient.

STANDARD OPERATING PROCEDURE FOR QUALITY CONTROL:
Assessments include weight and volume, pH, specific gravity, active drug assay, color, clarity, rheological properties such as pourability, physical observation and physical stability such as discoloration, foreign materials, gas formation and mold growth.

REGULATORY CONTROL:

…biodisponibilità…

Int J Paediatr Dent. 2001 Jan;11(1):33-40.
Intra-nasal midazolam in conscious sedation of young paediatric dental patients.
al-Rakaf H1, Bello LL, Turkustani A, Adenubi JO.
Author information

Abstract

OBJECTIVES:
To compare the effects of 3 different doses of intra-nasal midazolam in the conscious sedation of young paediatric dental patients and to compare the effectiveness of the sedation in the fasting and non-fasting child.
DESIGN:
Double blind random controlled trial.
SAMPLE AND METHODS:
Thirty-eight uncooperative young children aged 2-5 years (mean age 4.02 years) were randomly assigned to one of 3 groups. The groups and the doses of midazolam administered intra-nasally were A: 0.3 mg/kg, B: 0.4 mg/kg, and C: 0.5 mg/kg body weight. Each child in each group had two visits for restorative treatment: one without food (fasting) and the other with soft drink and light food (non-fasting) before treatment. Child behaviour and sedative effects were evaluated using the scoring system of Houpt. The vital signs were monitored continuously using a pulse oximeter and Dinamap machine.
RESULTS:
There was rapid onset of sedation with the maximal effect between 8 and 15 minutes. This sedation lasted for 25-40 minutes in Groups A and B and for 60 minutes in Group C. Conscious sedation and dental treatment were achieved in 79%, 96% and 100% of the children in Groups A, B and C, respectively. Consistently higher Houpt scores were seen in Groups B and C, with statistically significant differences between Groups A and C, and B and C (Tukey's range test, $P < 0.05$). There were no significant differences in the general behaviour of the child, the onset and the duration of sedation between the fasting and the non-fasting child (nonparametric ANOVA $P > 0.05$). All the vital signs were within normal physiological limits and there were no significant adverse effects either with or without fasting.
CONCLUSIONS:
All 3 doses of intranasal midazolam were effective in modifying the behaviour of the uncooperative child patient to accept dental treatment. This was irrespective of fasting.
PMID:
11309871

…composizione non uniforme…

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

Pharmacy

Drug Name	Route	Dosage Form	Concentration
Topiramate	Oral	Suspension	6mg/mL

Formula Qty: 100mL	Shelf Life: 90 days

Equipment needed:
Mortar, pestle, graduated cylinder, stirring rod

Auxiliary Labels/Storage: Shake Well; Refrigerate (preferred) or Room Temperature

Directions:

1. Place tablets in a mortar. Add a small amount of Ora-Plus and allow to sit for a few minutes to soften tablets.
2. Crush tablets and levigate to form a viscous, but smooth and uniform paste.
3. Continue adding Ora-Plus, geometrically, mixing well after each addition.
4. Transfer to a graduate.
5. Rinse mortar with Ora-Sweet, adding rinse to graduate.
6. QS to final volume with Ora-Sweet. Stir well.

Note: Consider using commercially available Topamax Sprinkles® instead of extemporaneously compounding the suspension. Do not use Ora-Blend; the vehicle does not produce a uniform suspension.

Ingredients	QS	Quantity	Units
Toprimate (Topamax®) 100mg Tablets		6	Tablets
Ora-Plus		50	mL
Ora-Sweet	X	100	mL

Citations/References

Nahata MC, Pai VB, Hipple TF. Topiramate. Pediatric Drug Formulations. 2004; (5): 282.

Reviewed: 6/4/2010 JEB

700 Children's Drive | Columbus, OH 43205

…cibo…

Isoniazid 10 mg/mL		
T = 0	100 ± 0.39	100 ± 0.39
T = 7	95.02 ± 0.37	99.37 ± 0.35
T = 14	93.49 ± 0.23	96.11 ± 0.30
T = 30	93.36 ± 0.27	93.68 ± 0.41
T = 60	94.02 ± 0.27	94.76 ± 0.81
T = 90	94.06 ± 0.45	93.89 ± 0.46

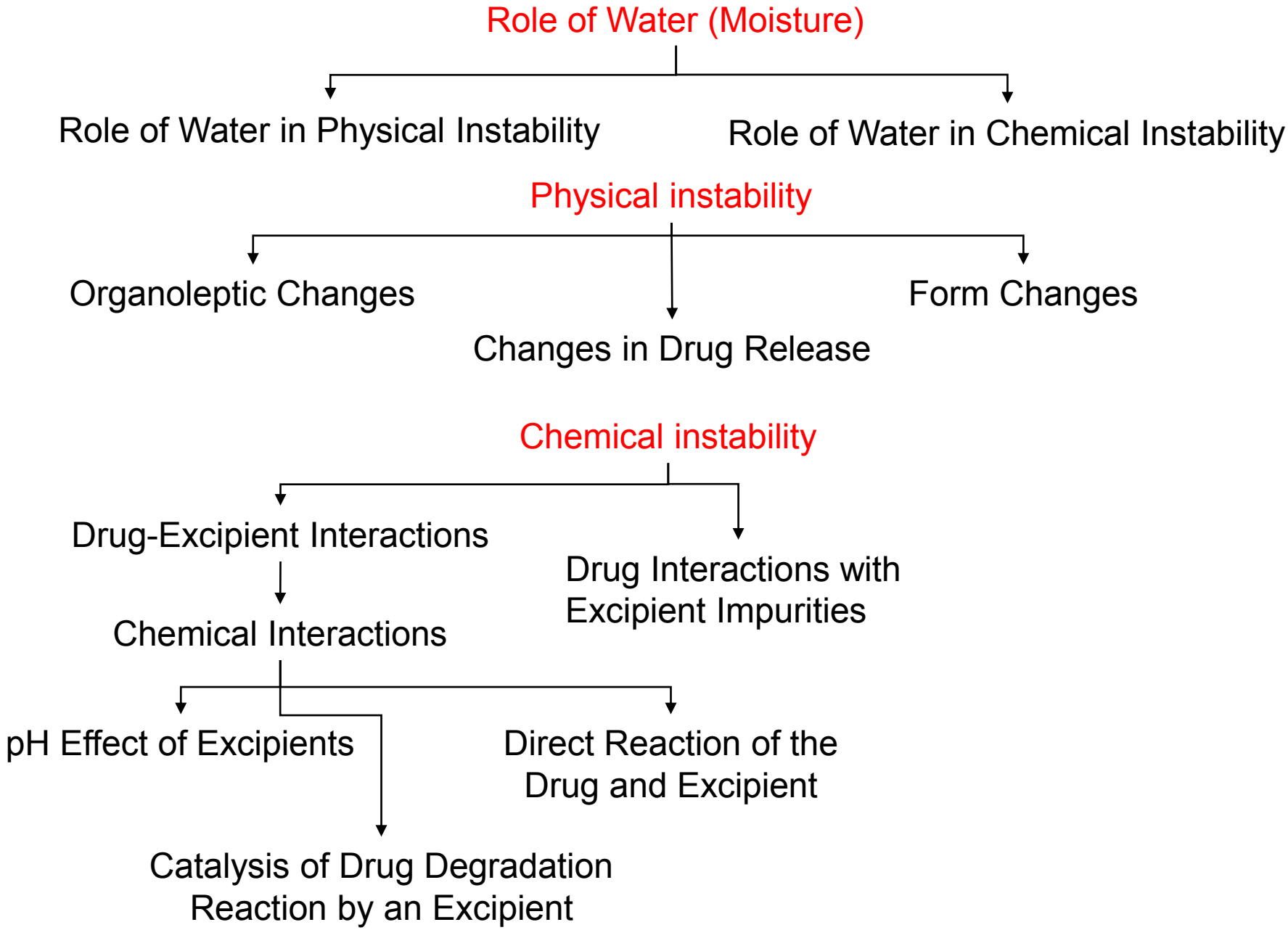
Diet Changes When Taking Isoniazid (INH)

Isoniazid (brand name Nydrazid) is an antibiotic medicine. It is most commonly used to prevent or treat tuberculosis. It is important that you take the medicine exactly as prescribed by your doctor.

There are some diet changes that you need to make to take this medicine safely. These changes will help prevent side effects and make the medicine work well in your body.

When You Take the Medicine

- Take this medicine on an empty stomach at least 1 hour before or 2 hours after eating. Food in your stomach decreases the amount of isoniazid your body can absorb.
- Do not drink alcohol when taking this medicine.
- Ask your doctor or pharmacist about taking a supplement of vitamin B6 (pyridoxine) while you take this medicine.
- Take vitamins, including vitamin B6 (pyridoxine), mineral supplements, or antacids separately at least 2 hours apart from this medicine.
- Increase your intake of folate (vitamin B9), niacin (vitamin B3) and magnesium while take isoniazid. Good food sources include: dark leafy greens, pinto or garbanzo beans, peanuts, Brazil nuts, almonds, cashews, asparagus, rice, wheat, flaxseed, molasses and cocoa powder.
- **Avoid foods that contain histamine** such as tuna, herring, mackerel, sardines, shellfish, anchovies, mushrooms, tomatoes, spinach, eggplant, and vinegar, or foods containing vinegar such as salad dressings and pickles.
- **Avoid foods that contain tyramine.** See the table on the next two pages for a listing of foods with tyramine.
- **Diet changes should be continued for 2 weeks after stopping isoniazid.**


Role of Water (Moisture)
Role of Water in Physical Instability
Role of Water in Chemical Instability
Physical instability
Organoleptic Changes
Form Changes
Changes in Drug Release
Chemical instability
Drug-Excipient Interactions
Drug Interactions with Excipient Impurities
Chemical Interactions
pH Effect of Excipients
Direct Reaction of the Drug and Excipient
Catalysis of Drug Degradation Reaction by an Excipient

Alcuni eccipienti di particolare interesse

Mucoadhesive polymer	Relevant properties
Chitosan	Natural polymer Soluble in acid solutions Cationic polymer Biodegradable High mucoadhesive properties (2,72,73)
Hydroxyethyl cellulose (HEC)	Semisynthetic and water soluble (temperature range 0–38°C) (2) Non-ionic polymer, fast rate of erosion, and high swelling (74) Chance for zero-order drug release kinetics (74)
Hydroxypropyl cellulose (HPC)	Semisynthetic, non-ionic, and water-soluble polymer Moderate swelling and slower rate of erosion compared with HEC (75)
Hydroxypropyl methylcellulose (HPMC)	Semisynthetic, non-ionic, and water-soluble polymer Rapid swelling, medium mucoadhesion, and chance for first-order drug release kinetics (76)
Guar gum and xanthan gum	Natural polymers Non-ionic Water-soluble polymers (77) High swelling (78)
Carboxymethyl cellulose (CMC)	Anionic polymer High swelling properties (79) High mucoadhesive properties (79)
Sodium alginate	Fast dissolution and erosion High swelling properties (66)
Poly(ethylene oxide)	Non-ionic polymer High mucoadhesive properties (80) with high concentrations of polymer (81) Zero-order release kinetics for cyclodextrine-loaded films (82)
Poly(vinyl pyrrolidone) (PVP)	Non-ionic (2) Improve elastic properties and film forming properties (83). High swelling properties (66)

Le fiabe non raccontano ai bambini

che i draghi esistono.

I bambini sanno già che i draghi esistono.

Le fiabe raccontano ai bambini

che i draghi possono essere uccisi.

Gilbert Keith Chesterton

Il gusto

… ma prima…

- Conoscere le vie di accesso
- Conoscere l’età e le abitudini del bambino
- Conoscere le terapie concomitanti

TASTE : SENSO CHIMICO

Il **senso del gusto** origina dall'interazione di molecole, presenti nel cibo o nelle bevande, che vengono introdotte nel cavo orofaringeo con le cellule sensoriali gustative, presenti per lo più sulla superficie della lingua, ma anche nel palato, nella faringe e nella laringe.

Le varie centinaia di sapori che è possibile percepire sono causate da **stimoli chimici**, che si possono raggruppare in base a **sei sapori principali**: *DOLCE, SALATO, ACIDO, AMARO, UMAMI (GUSTO DEL GLUTAMMATO), GUSTO DEL GRASSO.*

Il sistema gustativo, insieme a quelli olfattivo e chemiosensoriale trigeminale, è una **modalità chemiosensoriale**, cioè genera percetti in risposta a stimoli chimici.

DISFUNZIONI GUSTATIVE

-AGEUSIA: mancanza del gusto.
-IPOGEUSIA: diminuzione della sensibilità gustativa.
-IPERGEUSIA: eccessiva sensibilità gustativa.
-DISGEUSIA: alterazione del senso del gusto con distorsione delle percezioni dei sapori.
-ALLUCINAZIONI GUSTATIVE
- PERCEZIONE DI SAPORI ANCHE IN ASSENZA DI STIMOLI.

Farmaci quali Captopril e Penicillamina (hanno gruppi sulfidrilici) causano una temporanea perdita della sensazione gustativa.

VARIAZIONI ED EFFETTI POSTUMI

Il senso del gusto a volte mostra reazioni ritardate e fenomeni di contrasto per la base chimica locale o per fenomeni centrali.

È stata scoperta in una pianta una proteina, la miraculina che, applicata sulla lingua, fa sentire dolce l'acido.

SOGLIA PER IL GUSTO

La concentrazione-soglia di una sostanza alla quale le papille gustative rispondono varia da sostanza a sostanza.

DISCRIMINAZIONE DELL'INTENSITÀ

È relativamente grossolana, la concentrazione della sostanza deve variare di almeno il 30% prima di ottenere una differenza di intensità

Farmacovigilanza…

Tabella I. Definizioni delle alterazioni gustative

Alterazioni qualitative

Il termine **disgeusia** definisce una distorsione della percezione gustativa. Questa alterazione viene chiamata **parageusia** quando sopravviene nel corso della alimentazione (o della bevanda), e **fantageusia** quando sopravviene in assenza dello stimolo gustativo, che sia in modo costante o intermittente. In quest'ultimo caso, si può tuttavia constatare talvolta un aumento dei sintomi durante l'alimentazione.

Il termine **eterogeusia** definisce la condizione in cui il gusto, senza essere spiacevole, può risultare inabituale, inatteso, come quando, per esempio, un alimento zuccherato è percepito salato. Si parla di **cacogeusia** quando un gusto è percepito come pessimo.

Alterazioni quantitative:

Si parla di **ageusia** quando la sensazione del gusto sparisce totalmente; di **ipogeusia** quando la sensazione del gusto è diminuita e di **ipergeusia** quando la sensazione del gusto è aumentata.

Si usa il termine "**dissociato**" quando solo alcuni sapori sono alterati [6-7]. Il danno è detto "**specifico**" quando non possono essere percepite solo alcune sostanze di un dato tipo, "**parziale**" quando solo alcuni campi gustativi sono interessati [8].

Tabella II. Farmaci dell'apparato cardiovascolare che hanno indotto turbe del gusto

Farmaco	N.o report	Effetti osservati	Imputabilità
ACE-inibitori	45	Ageusia, disgeusia, ipogeusia	33 certe, 12 plausibili
Calcio-antagonisti	10	Ageusia, disgeusia	9 certe, 1 plausibile
Beta-bloccanti	10	Ageusia, disgeusia, ipogeusia	9 certe, 1 plausibile
Propafenone	6	Ageusia, disgeusia	2 certe, 2 plausibili, 2 verosimili
Amiodarone	4	Ageusia, disgeusia	3 certe, 1 plausibili
Anticoagulanti orali	9	Ageusia, disgeusia	6 certe, 1 plausibili, 2 verosimili
Eparine	3	Ageusia, disgeusia	2 certe, 1 plausibili
Molsidomina	1	Ageusia	1 verosimile

http://www.farmacovigilanza.org/corsi/corso_20010915.02.htm

Farmacovigilanza…

Tabella III. Farmaci antiinfettivi che hanno indotto turbe del gusto			
Farmaco	**N.o report**	**Effetti osservati**	**Imputabilità**
Terbinafina	31	Ageusia, disgeusia, ipogeusia	21 certe, 7 plausibili, 3 verosimili
Imidazoli	12	Ageusia, disgeusia	7 certe, 2 plausibile, 3 verosimili
Meflochina	2	Ageusia	1 certa, 1 plausibile
Macrolidi	11	Ageusia, disgeusia, ipogeusia	5 certe, 2 plausibili, 4 verosimili
Chinoloni	11	Ageusia, disgeusia, ipogeusia	8 certe, 1 plausibile, 2 verosimili
Nitrofurantoina	1	Disgeusia	1 verosimile
Zidovudina	6	Ageusia, disgeusia	5 certe, 1 plausibile

Farmacovigilanza…

Tabella IV. Farmaci antiinfiammatori che hanno indotto turbe del gusto			
Farmaco	**N.o report**	**Effetti osservati**	**Imputabilità**
D-penicillamina e simili (tioprolina e piritimol)	17	Ageusia	11 certe, 5 plausibili, 1 verosimile
Idrossiclorochina	4	Ageusia, ipoegusia	3 certe, 1 plausibile
Sali d'oro	2	Ageusia	1 certa, 1 verosimile
FANS	7	Ageusia, disgeusia	5 certe, 1 plausibili, 1 verosimile
Aspirina	3	Ageusia, disgeusia	3 certe
Cortisonici	6	Ageusia, ipogeusia	6 certe

Tabella V. Farmaci del SNC che hanno indotto turbe del gusto			
Farmaco	**N.o report**	**Effetti osservati**	**Imputabilità**
Zoplicone	18	Ageusia, disgeusia	3 certe, 9 plausibili, 6 verosimili
Zolpidem	3	Ageusia, disgeusia	3 certe
Carbamazepina	6	Ageusia, disgeusia	5 certa, 1 plausibile
Imipramina	3	Disgeusia	3 certe
Apomorfina	3	Ageusia	3 certe

Farmacovigilanza…

Tabella VI. Farmaci dei sistemi endocrino e metabolico che hanno indotto turbe del gusto

Farmaco	N.o report	Effetti osservati	Imputabilità
Carbimazolo	10	Ageusia, disgeusia	6 certe, 4 plausibili
Propiltiuracile	4	Ageusia, disgeusia	4 certe
Statine	5	Ageusia, disgeusia	3 certa, 2 plausibile
Fibrati	5	Ageusia, disgeusia	4 certe, 1 verosimile
Calciferolo	1	Disgeusia	1 verosimile
Tetracosactide	1	Disgeusia	1 verosimile

Tabella VII. Farmaci antineoplastici ed immunosoppressori che hanno indotto turbe del gusto

Farmaco	N.o report	Effetti osservati	Imputabilità
Antineoplastici • Metotrexate • Ciclofosfamide • Epirubicina • Tamoxifene • Cloraminofene • Bleomicina	6 *(con insorgenza tra 2 settimane e 3 anni)*	Ageusia, disgeusia,	5 certe, 1 plausibile *(3 casi sono regrediti spontaneamente)*
Ciclosporina	3	disgeusia	3 certe

Tabella VIII. Farmaci dell'apparato gastroenterico, del sistema respiratorio ed anestetici locali che hanno indotto turbe del gusto

Farmaco	N.o report	Effetti osservati	Imputabilità
Sulfasalazina	4 *(con insorgenza tra 7 settimane e 5 mesi)*	Ageusia, disgeusia	2 certe, 1 plausibile, 1 verosimile *(3 casi regrediti spontaneamente)*
Domperidone	1	Ageusia	1 verosimile
Beta2-stimolanti	3	Ageusia, ipogeusia	3 certe
Teofillina e derivati	3	Ageusia, disgeusia	3 certe
Mucolitici	3	Ageusia, ipogeusia	3 certe
Anestetici locali	6 *(con insorgenza da 24 ore a 4 giorni)*	Ageusia, disgeusia	2 certe, 4 verosimili *(5 casi regrediti spontaneamente)*

Quali mezzi?

- Come già detto per molti pazienti, pediatrici, geriatrici… la forma farmaceutica migliore è quella LIQUIDA

Pro:	Contro:
Facilità di somministrazione	Carenza studi stabilità
Modulazione della dose	Carenza p.a.
No rischio soffocamento	Gusto!
…	…

1 concetto base:

Si fa quel che si può! Quando si allestisce una soluzione, non è sempre possibile mascherare completamente tutti gli attivi.

Gli aromi

ANTIBIOTICI

Cherry, maple, pineapple, orange, raspberry, banana-pineapple, banana-vanilla, coconut-custard, strawberry-vanilla, lemon-custard, cherry custard, fruit-cinnamon

ANTISTAMINICI

Apricot, black currant, cherry, cinnamon, custard, grape, honey, lime, loganberry, peach-orange, peach-rum, raspberry, root beer, wild cherry

BARBITURICI

Banana-pineapple, banana-vanilla, black currant, cinnamon-peppermint, grenadine-strawberry, lime, orange, peach-orange, root beer

DECONGESTIONANTI/ESPETTORANTI

Anise, apricot, black-currant, butterscotch, cherry, coconut-custard, custard-mint-strawberry, grenadine-peach, strawberry, lemon, gooseberry, loganberry, maple, orange, orange-lemon, coriander, orange-peach, pineapple, raspberry, strawberry, tangerne

ELETTROLITI

Cherry, grape, lemon-lime, raspberry, wild cherry syrup

ANTIACIDI

Mint, peppermint, spearmint, raspberry-mint, strawberry-mint

ANTIEMETICI

Any creamy flavor such as vanilla, custard, or marshmallow. Some patients like it combined with banana

Gli edulcoranti

Table 1: Relative sweetness of commonly used sweeteners [7]

Sweetening Agents	Relative Sweetness *	Comment
Aspartame	200	Not very stable in solution
Acesulfame potassium	137-200	Bitter after taste if used in higher concentration
Cyclamate	40	Banned
Glycerrhizin	50	Moderately expensive
Lactose	0.16	Large amount required
Manitol	0.60	Negative heat of solution
Saccharin	450	Unpleasant after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergestic sweetening effect

*Sucrose is taken as a standard of 1 for comparison

(1) Nutritive Sweeteners:

- Sucrose
- Glucose
- Dextrose
- Fructose

(2) Non Nutritive Sweeteners:

Table 1 Sweetness factors of Different Sweeteners	
Sweeteners	**Sweetness factor, Sucrose=1**
Aspartame	180-200
Sucralose	600
Acesulfame K	200
Neotame	7,000-13,000
Saccharin	300

…ma facciamo attenzione ad alcuni…

Edulcorante	Pro	Contro
Saccarosio	•Edulcorante per antonomasia, descritto nella > parte delle formulazioni	•Evitare in caso di intolleranza ereditaria al fruttosio •Diabete •Cariogeno
Fruttosio	•Fino a 70% più dolce del saccarosio	•Effetto lassativo se in dosi elevate •Controindicato in pazienti con ipoglicemia •Elevato apporto calorico •Vedi saccarosio
Sorbitolo, xilitolo	•No assorbimento intestinale>> ok per diabetici •Xilitolo percezione freschezza, acariogeno	•Effetto osmotico a livello intestinale •Sorbitolo viene convertito in fruttosio>>vedi sopra
Aspartame	•200 volte il saccarosio	•Instabile in soluzione •Dipeptide dell'acido aspartico e metilestere della fenilalanina, controindicato in pazienti con fenilchetonuria (autosomica recessiva) •Sintomi: mal di testa, nervosismo, rare le reazioni da ipersensibilità
Saccarina	•450 volte il saccarosio •Non è genotissica	•Ad alte concentrazioni retrogusto amaro e metallico •Reazioni da ipersensibilità, più frequentemente frequentemente dermatologiche (prurito, orticaria, eczema) dermatologiche (prurito, orticaria, eczema) •bambini con allergia ai sulfonamidi sulfonamidi devono evitare la saccarina

Caratteristiche di alcuni edulcoranti

Chi	Cosa	Concentrazione utilizzata (%)	Potere edulcorante vs saccarosio
Acesulfame potassico	is an intense sweetening agent and flavor enhancer that can be effectively used to mask some unpleasant tastes. It occurs as a colorless to white-olored, odorless, crystalline powder with an intensely sweet taste. It is quite stable in the solid state,in solution and at elevated tem peratures. Synergism with other sweeteners has been effectively used,especially with aspartame or sodium cyclamate.	0,3-0,5	180-200
Aspartame	is an off-white, almost odorless crystalline powder with an intensely sweet taste. In aqueous solutions, its solubility actually increases with a decrease in pH and an increase in temperature. It is stable when dry but can hydrolyze in the presence of moisture. In solution, its stability is improved by the addition of cyclodextrins to the formulation. It also degrades during prolonged heating; this can be minimized by using higher temperatures for short time periods,followed by rapid cooling. Aspartame can be used synergistically with saccharin, sucrose, glucose and cyclamate and its taste can actually be enhanced with sodium bicarbonate, gluconate salts and lactose. It does not have the aftertaste associated with saccharin, but it does have a pH/temperature-dependent stability profile.	0,1-0,5	200
Ciclammato di calcio	is a white crystalline powder with a sweet-sour taste. It is used as a nonnutritive low-calorie sweetener choice (but prohibited in some countries due to possible carcinogenic effects of its metabolic products). It is soluble in water and in ethanol. It is known about 30 times sweeter than sucrose.	0,17	30
Stevia	is the extract of the plant *Stevia rebaudiana*. It is a white crystalline powder and usually ranges anywhere from 250 to 300 times sweeter than table sugar (sucrose). It does not affect sugar metabolism. This extract is non-nutritive; does not contribute calories to diet. It may be heated with no adverse reactions to the chemical. It is classified as a food ingredient and the extract usually contains 90% of stevioside.	<0,03	300

i potenziatori del gusto

- Aggiunti all'edulcorante
- Aumentano la percezione di dolcezza dell'edulcorante
- Mascherano o competono con il gusto amaro
- Generalmente acidi carbossilici (citrico, malico, tartarico), alcuni Sali (NaCl), ed amino derivati (glutammato di sodio)

Alcuni esempi

Table 4: Enlists various taste suppressants and potentiators used for taste masking [42-47]

Drug	Category	Taste suppressant and / potentiator used
Bromhexine	Mucolytic	Thaumatin and sugar
Caffeine	Diuretic	Hydroxyflavones
Caffeine	Diuretic	Gamma-amino butyric acid
Paracetamol	Antipyretic	Poteniators: Glycyrrhizin, Thaumatin and neohesperidine dihydrochalcone(NHDC) Sweeteners: Saccharin salts, acesulfame etc
Pioglitazone	Anti diabetic	Sodium chloride and coating with saccharides
Sugar alcohol	Nutritive agent	Aldehydes (citral dimethyl acetal) and flavours

Gli enhancer

ANCILLARY AGENTS IN MASKING TASTE

Citric acid, USP
anhydrous: $C_6H_8O_7$, MW 192.12
monohydrate: $C_6H_8O_7 \cdot H_2O$, MW 210.14
Occurs as colorless, translucent crystals or as a white, granular to fine, crystalline powder. It should be labeled to indicate whether it is anhydrous or hydrous; it is used as an acidifying agent, an antioxidant, a buffering agent, a chelating agent, and a flavor enhancer. It has three pKa values (3.128, 4.761, and 6.396). It is listed as incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides; and it is incompatible with oxidizing agents, bases, reducing agents, and nitrates.

Ethyl Maltol, ($C_7H_8O_3$, MW 140.14)
Occurs as a white crystalline solid with a characteristic, very sweet, caramel-like odor and taste. When in a dilute solution, it possesses a sweet, fruit-like flavor and odor.

Ethyl Vanillin, NF, ($C_9H_{10}O_3$,MW 166.17, bourbonal, ethylprotal, vanillal)
Occurs as fine, white or slightly yellowish crystals; its taste and odor are similar to that of vanillin. It is light sensitive, and solutions of ethyl vanillin are acid to litmus. It is freely soluble in solutions of alkali hydroxides. Its flavor and odor are about 3 times as intense as those of vanillin. In higher than recommended concentrations, it may impart an unpleasant, slightly bitter taste to a product because of its intensity. It is incompatible on contact with iron or steel, at which time a red flavorless compound forms. It produces a yellow color when used with neomycin sulfate or succinylsulfathiazole.

Fumaric Acid, NF, ($C_4H_4O_4$, MW 116.07, allomaleic acid, boletic acid, lichenic acid)
Occurs as white odorless granules or as a crystalline powder. Fumaric acid is used as an acidulant, an antioxidant, a flavoring agent, and a therapeutic agent. It has two pKa values (3.03 and 4.54), and its incompatibilities are those typical of an organic acid.

Malic acid, NF ($C_4H_6O_5$,MW 134.09, apple acid)
occurs as a white or practically white crystalline powder or granules and has a strongly acid taste. It is used as an acidulant, an antioxidant, a flavoring agent, a therapeutic agent, a chelating agent, and a buffering agent. It possesses a slight apple flavor and can be used as a flavoring agent to mask bitter tastes and provide tartness. It is also used as an alternative to citric acid. Malic acid used in the United States and Europe is a racemic mixture, but that occurring in apples and fruits is levorotatory. It has two pKa values (3.40 and 5.05). It is listed as incompatible with oxidizing materials, and its aqueous solutions are mildly corrosive to carbon steels.

Maltol, ($C_6H_6O_3$, MW 126.11)
occurs as a white crystalline solid with a characteristic caramel-like odor and taste. It has a sweet strawberry-like or pineapple-like flavor and odor in dilute solution. In concentrated solutions, it is listed as incompatible with metal containers, which it may discolor during storage.

Menthol, USP ($C_{10}H_{20}O$, MW 156.27, peppermint camphor, racemic menthol)
Occurs as a crystalline powder or as colorless hexagonal crystals that are usually needlelike or are in fused masses. It has a pleasant peppermint like odor. It should be labeled to indicate whether it is levorotatory or racemic. Menthol is used as a flavoring agent or an odor enhancer. The cooling effect of menthol is due to its l-menthol component; d-menthol has no cooling effect, and racemic menthol has an effect approximately half that of l-menthol. Menthol is listed as incompatible with ß-napthol, butylchloral hydrate, camphor, chloral hydrate, chromium trioxide, phenol, potassium permanganate, pyrogallol, resorcinol, and thymol.

Monosodium glutamate, NF ($C_5H_8NNaO_4 \cdot H_2O$)
Occurs as white, practically odorless, free-flowing crystals or as a crystalline powder. It is prepared from the fermentation of beet sugar or molasses or by the hydrolysis of vegetable proteins. It may have either a slightly sweet or a slightly salty taste. Maximum daily intake should not exceed 120 mg in adults and children older than 12.

Sodium chloride, USP (NaCl, MW 58.55, common salt, natural halite, rock salt, salt, sea salt, table salt)
Occurs as colorless cubic crystals or as a white crystalline powder with a saline taste. Aqueous solutions of sodium chloride are corrosive to iron and react with silver, lead, and mercury salts to form precipitates. Chlorine can be liberated from acidified solutions by strong oxidizing agents. Sodium chloride can decrease the solubility of methylparaben in aqueous solutions, and the viscosity of carbomer gels and solutions of hydroxyethyl cellulose or hydroxypropyl cellulose is reduced in its presence.

Tartaric acid, NF ($C_4H_6O_6$, MW 150.09)
Occurs as colorless or translucent crystals or as a white, fine to granular, crystalline powder. It is odorless, has an acid taste, and is stable in air. Tartaric acid is used as an acidifying agent, an acidulant, a flavor enhancer, and a sequestering agent. It has two dissociation constants (2.93 and 4.23). Incompatibilities include silver, metal carbonates, and bicarbonates.

Vanillin, NF ($C_8H_8O_3$, MW 152.15)
Occurs as fine white to slightly yellow crystals that are usually needle-like and have an odor and taste similar to those of vanilla. It is widely used as a flavor in pharmaceuticals; in solutions, it is usually used in a 0.01%-0.02% w/v concentration to mask the unpleasant taste or odor of certain formulations. It is also used in the film coatings of certain vitamin tablets to mask an unpleasant odor and taste. It is affected by light, and solutions of vanillin are acid to litmus. It is listed as incompatible with acetone, with which it forms a brightly colored compound. When mixed with glycerin, a compound that is practically insoluble in ethanol is formed.

Esempi farmaci in commercio con indicazione pediatrica

- Onli peg (acesulfame k)
- Tachipirina sciroppo (macrogol 6000)
- Hemangiol (saccarina)
- Momentkid (parabeni)

Take home message

- La soluzione migliore è: la Soluzione
- Più è semplice allestirla, meno rischi corro
- Se ho studi di stabilità disponibili devo riprodurre pedissequamente la formulazione
- E’ importante il gusto, ma di più la terapia
- Conosciamo i nostri pazienti
- Dialoghiamo con il pediatra

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