Everlasting problem with paediatric forms for pain control

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Therapeutical booklet of pediatric painkillers: historical delay

- Insufficient marketing authorization
- Not documented clinical assessment
- Incomplete pharmacological and pharmacokinetic studies
- **Unadapted, limited galenic forms and dosages**
3 steps WHO ladder

1. Pain
   - Non opioid ± Adjuvant

2. Pain persisting or increasing
   - Opioid for Mild to Moderate Pain
   ± Non opioid ± Adjuvant

3. Freedom from pain
   - Opioid for Mild to Severe Pain
   ± Non opioid ± Adjuvant
# Painkillers authorised for children in France

<table>
<thead>
<tr>
<th>Newborn 0 - 28 days</th>
<th>Infant 1 month – 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months</td>
</tr>
<tr>
<td><strong>STEP I</strong></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen PO et IV + Ibuprofen PO</td>
<td>+ Aspirin PO</td>
</tr>
<tr>
<td><strong>STEP II</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>STEP III</strong></td>
<td></td>
</tr>
<tr>
<td>Morphine IV Fentanyl IV&lt;sub&gt;H&lt;/sub&gt;</td>
<td>Idem</td>
</tr>
</tbody>
</table>

<sup>H</sup>: hospital
# Painkillers authorised for children in France (2)

<table>
<thead>
<tr>
<th>Child 2 years – 12 years</th>
<th>Teenager 12 years – 15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30 months</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen PO et IV</td>
<td>+ Niflumic Acid PO</td>
</tr>
<tr>
<td>Aspirin PO</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen PO</td>
<td>+ Niflumic Acid PO</td>
</tr>
<tr>
<td>Niflumic acid Suppo.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Niflumic Acid PO</td>
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<tr>
<td>&gt; 4 years</td>
<td></td>
</tr>
<tr>
<td>+ Tiaprofenic Acid PO</td>
<td>+ Niflumic Acid PO</td>
</tr>
<tr>
<td></td>
<td>+ Niflumic Acid PO</td>
</tr>
<tr>
<td>+ Diclofenac suppo., PO</td>
<td></td>
</tr>
<tr>
<td>+ Naproxene PO</td>
<td></td>
</tr>
<tr>
<td>(25 kg = 8 years ?)</td>
<td></td>
</tr>
<tr>
<td>&gt; 7 years</td>
<td></td>
</tr>
<tr>
<td>+ Acetaminophen PO</td>
<td></td>
</tr>
<tr>
<td>+ Aspirin PO</td>
<td></td>
</tr>
<tr>
<td>+ Ibuprofen PO</td>
<td></td>
</tr>
<tr>
<td>+ Niflumic acid Suppo.</td>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Codeine PO</td>
<td>Nalbuphine I</td>
<td>Morphine IV</td>
<td>Fentanyl IV ^H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idem</td>
<td>Idem</td>
<td>Idem</td>
<td>Idem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ Buprenorphine PO</td>
<td>+ Hydromorphone PO</td>
<td>+ Idem</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>+ Oxycodone</td>
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</tbody>
</table>

^H : hospital
# Marketed dose forms

<table>
<thead>
<tr>
<th>Oral solid forms</th>
<th>Oral liquid forms</th>
<th>Suppositories</th>
<th>Injectable forms</th>
<th>TDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Scored Y/N</td>
<td>Solution</td>
<td>Scored Y/N</td>
<td>Bottle</td>
<td>Matrix</td>
</tr>
<tr>
<td>▪ Chewable</td>
<td>Suspension</td>
<td></td>
<td>Ampoule</td>
<td></td>
</tr>
<tr>
<td>▪ Coated, scored Y/N</td>
<td>Syrup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ SR</td>
<td>Powder and granule for oral solution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Effervescent scored Y/N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Capsule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ SR capsule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Orodispersible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Dispersible</td>
<td></td>
<td></td>
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</tbody>
</table>

Unapproved dose forms already widely used

Daily use forms with some issues

Forms to be developed
Unapproved dose forms already widely used!!! (1)

CHILDREN
≤ 6 years

Tablets
± Scored

usual
chewable
film coated
sugar coated

± long acting
not to divide

Sugar coated = sieved!
Unapproved dose forms already widely used!!! (2)

PEDIAAD : Tablets

- Cut tablets : 46,7 %
- Crushed tablets : 74,2 %
- Crushed tablets are mixed with a drink (96,4 %) or food (3,6 %)
Unapproved dose forms already widely used!!! (3)

**PEDIAAD : Tablets**

- Not administered part is kept: 44.2%

- This part is administered
  - To the same patient: 67.6%
  - To another patient: 32.4%

- Tablets dissolved in water and proportion is taken: 34.7%
Daily used forms:
the best of the worst!!(1)

1- Scored or not effervescent tablets
2- Capsules
3- Powder and granule for oral solution
4- Oral liquid forms: Solution, Suspension, Syrup
5- Scored or not suppositories
6- Injectable forms
Daily used forms:  
the best of the worst!! (1)

**Habit:**
- dissolve in a given volume of water
- take a proportion of the solution equivalent to the prescribed dose: lack of precision
- keep the solution in fridge
- Instability and contamination risk

**Problem:**
- sodium content
- gastroesophageal reflux risk
Daily used forms: the best of the worst!! (1)
Sodium in effervescent tablets

- **Acetaminophen**
  - Claradol®: 422 mg Na/ 500mg
  - Doliprane® 408 mg Na/ 500 and 1000mg
  - Efferalgan® 412,4 mg Na/ 500mg

- **Aspirine**
  - aspirine UPSA® 388,5 mg Na/ 500mg

- **Ibuprofène**
  - Upfen® 150 mgNa/ 200mg

Regurgitation, nausea, vomiting
Daily used forms: the best of the worst!!(2)

1- Scored or not effervescent tablets

2- Capsules

3- Powder and granule for oral solution

4- Oral liquid forms: Solution, Suspension, Syrup

5- Scored or not suppositories

6- Injectable forms
Daily used forms:
the best of the worst!!(2)

Actiskénan® gel $\geq$ 6 months
Skénan® LA gel $> 6$ months
Kapanol® LA gel $?$
Sevredol® cp $> 6$ years
Moscotin® LA cp $> 6$ years

Rationalize the AMM of oral solid forms

Don’t divide the powder into 2 or 3 parts

Pédiad : 67 % of capsules were prepared by the pharmacy
Most of them were opened when nasogastric tubes are used.
Daily used forms:
the best of the worst!!(3)

1- Scored or not effervescent tablets

2- Capsules

3- Powder and granule for oral solution

4- Oral liquid forms: Solution, Suspension, Syrup

5- Scored or not suppositories

6- Injectable forms
Daily used forms: 
the best of the worst!!(3)

- Use a spoon or a glass or a teat, never use a feeding bottle
- always put the powder at the bottom of the glass and pour the liquid

Risk: to loose a part of the powder of the small sachets, necessary to rinse the sachet
Daily used forms: the best of the worst!!(3)
sucrose in sachets

- **Acetaminophen**
  - 2g sucrose/ 500mg
  - Or aspartam

+ Sweeteners and flavourings to improve the taste
  excipients with notorious effect
Daily used forms: the best of the worst!!!(4)

1- Scored or not effervescent tablets
2- Capsules
3- Powder and granule for oral solution
4- Oral liquid forms: Solution, Suspension, Syrup
5- Scored or not suppositories
6- Injectable forms
Daily used forms:
the best of the worst!!!(4)

1mg/mL
MA = 12 months
Usable from 1 to 4 years
Beyond inadapted volume:
15 mL/ intake!

2 to 4 mg/kg/day
Daily used forms: the best of the worst!!!(4)
Require precise medical devices

> **3 kg** Pipette graduated with a 0.5 kg interval

> **4 kg** Spoon graduated with a 2 kg interval
Daily used forms: the best of the worst!!!(4)  
Require precise medical devices

Aguettant 5 mg/mL + Pipette:
first graduation = 2.5 mg
0.5 mg interval

Pain: 0.20 mg/kg/intake
6 months = 7 kg:
1.4 mg/intake

#0.3mL = IMPOSSIBLE
Daily used forms: the best of the worst!!!(4)
Compulsary safety caps and tamper evident!

In reality white letters on a white background

Can you open them?

Name of the drug on the caps and the devices

Appealing leaflet
Daily used forms: 
the best of the worst!!!(4) 
Sucrose

– 25%, sucrose bottle of 10 mL

– Administered 2min before any care with a teat

– Mechanism: endorphins are freed till Day 28

– Indications limited
  • osmolarity and ECUN risk
  • Fructose related allergy
  • Bad habit forming
Daily used forms: 
the best of the worst!!!(4)

Tramadol, in Europe

Are we talking about free exchange?

Daily used forms: the best of the worst!!!(4)

Tramadol = Topalgic®

To hold vertically! To prescribe in mg and drops!
Daily used forms: the best of the worst!!!(5)

1- Scored or not effervescent tablets

2- Capsules

3- Powder and granule for oral solution

4- Oral liquid forms: Solution, Suspension, Syrup

5- Scored or not suppositories

6- Injectable forms
Daily used forms: the best of the worst!!!(5)
Suppositories

- First pass metabolism
- Administration not easy for scored suppositories
Daily used forms: the best of the worst!!!(6)

1- Scored or not effervescent tablets

2- Capsules

3- Powder and granule for oral solution

4- Oral liquid forms: Solution, Suspension, Syrup

5- Scored or not suppositories

6- Injectable forms
Daily used forms: the best of the worst!!!(6)

Injectable forms

- **Perfalgan®** injectable (10 mg/ml, bottle of 50 ml = 500mg)

- Dose: 15 mg/kg x 4/d-injection (1.5mL) 15 min

- **is not adapted to newborns and infants** all the more as it must not be diluted

_Do not give any marketing authorization without data of form or dosage_
Daily used forms:
the best of the worst!!!(6)
Injectable forms

- Injectable morphine:
  lots of formulations:
  1 to 250 mg

- Double end ampoule

- Concentration expressed as percentage
Forms to be developed (1)

- **Oral lyophilisate** → Paralyoc® 250 mg 13 kg to 26 kg (2 to 8 years old)
  → Spasfon® 80 mg child?

- **Mouth dispersible** → Solupred 5mg C > 10 kg

- **Dispersible** → Celestène 0,5mg C > to 6 years old
Forms to be developed (2)

What is ACTIQ?

fentanyl Citrate

drug/tablet

End for handling

plastic stick/Device
Forms to be developed (3)

TDDS = transdermal drug delivery system

EMLA

0-3 months: 1 hour application max after : 1 to 4 hours application

FENTANYL
Pharmaceutical firms do not meet the needs of children.
They must be encouraged to develop appropriate paediatric dose forms.
Conclusion (2)

- We must identify appropriate paediatric medicines authorised in one European country and ensure their availability in all others.
- Pharmaceuticals companies should declare to EMEA what they have commercialised in each country.
Paediatricians should choose authorised drug with appropriate dose form whenever possible.

Paediatricians should only prescribe an extemporaneous preparation if there is no alternative with a standard dosage by range of age.