ARBOP-P: A practical framework for the Assessment of Risks and Benefits of Off label Prescribing in Paediatrics

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INTRODUCTION

- Emerging guidelines on off-label use focus on high quality evidence
- High level of evidence often lacking in paediatrics, therefore different approach is needed.

AIM: Provide practical guidance on how to assess and balance the benefits and risks for off-label use and how to select the right pediatric dose.

METHODS

A. Literature review on suggested criteria for appropriate off-label use. Evaluate criteria for applicability and relevance in paedatrics

B. Literature review for strategies to asess risks and benefits of off-label use. Develop framework. Apply the framework to a case

RESULTS

A. CRITERIA FOR APPROPRIATE OFF-LABEL USE IN PAEDIATRIC PATIENTS

1. **Identification of the medical need.** Ensuring that all treatment options –licensed as well as off-label- are given due consideration.
2. **Off-label use is based on 'high quality evidence'.** As 'high quality evidence' in pediatrics is often lacking, we propose to replace the need for 'high quality evidence' by a positive risk-benefit assessment based on available evidence.
3. **Parents and patients are informed.** in general parents and patients need to be informed about risks and benefits of the proposed drug treatment, irrespective of the label of use. If the off-label use is based on high quality evidence, no additional informed consent beyond that routinely used in therapeutic decision making is needed.
4. **The outcomes of off-label use are followed up.**

B. HOW TO ASSESS THE RISKS-BENEFITS OF OFF-LABEL PRESCRIBING in PAEDIATRICS (ARBOP-P)

Based on the PRO-ACT-URL[1] and FDA pediatric decision tree on extrapolation of data[2]

1. **Identify medical need** Ensuring that all treatment options –licensed as well as off-label- are given due consideration.
   (do no proceed to step 2 if medical need is lacking)
2. **Check if off-label use is recommended by peer-reviewed clinical guidelines or referenced drug handbooks.**
   (*do not proceed to step 3 if off-label use is recommended by guidelines or drug handbooks)*
3. **Identify risks and benefits based on available evidence**
   I. What is known about the drug in adults: mechanism of action, efficacy, safety and pharmacokinetics, including concentration-response?
   II. What is known about the drug in children? Can we assume a similar mechanism of action and exposure-response relationship in children compared to adults? If not, what exposure is aimed for in children?
   III. What is known about the pharmacokinetics in children? How can we extrapolate the adult dose to children? Which dose would be expected to result in the desired outcome.
   IV. What is known about safety? What risks can be expected? Are these risks dose dependent? How can these risks be prevented, minimized or monitored?
4. **Identify *assumed* and unknown risks and benefits.** What critical questions remain unanswered by literature?
5. **Balance the identified benefits versus the risks.** Are the benefits clinically relevant? Are the risks acceptable? In light of the identified risks, are the alternative treatment options still considered unsuitable?
6. **Assess the quality of the evidence considered.** A positive risk benefit ratio does not require a minimal level of evidence. However a low level of evidence should be considered being a risk. The extent to which one can be confident that the off-label use will do more good than harm.
7. **Complement available evidence with clinical experience and consensus.** Attitudes and expert opinions are explicit. Consider bias and conflicts of interest of team members involved in the risk-benefit assessment.
8. **DO THE BENEFITS OUTWEIGHT THE RISKS?**

CASE

We applied the framework in retrospect to a case where sirolimus was used off-label in 3-month-old patient with kaposiform hemangioendothelioma with Kasabach-Merritt Phenomenon (KMP). The lesion improved quickly, but ultimately the patient died due to an initially unrecognized interstitial pneumonitis, likely related to high concentrations of sirolimus. Application of the ARBOPP framework revealed a well-known pathogenesis of the condition and mechanism of action of the drug, a decreased clearance of the drug due to age related Cyp3A4 maturation and dose related toxicity. Common side effects are mild and can be managed by dose adjustments. Serious side effects include pulmonary toxicity (sirolimus associated pneumonitis) that may be fatal if not recognized. Dose should adapted in line with Cyp3A4 maturation of the infant

CONCLUSIONS

We identified important aspects and tools to develop a framework to guide healthcare professionals on how to systematically assess and balance the benefits and risks for off-label use, including dose selection, to ultimately optimize efficacy and safety of pediatric off-label prescribing.

READ IT LATER?

1. Hammond J, Keeney R, Raiffa H. Smart Choices: A Practical Guide to Making Better Decisions. . Boston, MA.: Harvard Business School Press.; 2002

2. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011 Nov;128(5):e1242-9.