Ocular medicines in children: the regulatory situation related to clinical research

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Abstract

Background: Many ocular medications are prescribed for paediatric patients, but the evidence for their rational use is very scant. This study was planned to compare the availability and the licensing status of ocular medications marketed in Italy, the United Kingdom (UK), and the United States of America (USA) related to the amount of published and un-published RCTs testing these drugs in the paediatric population.

Methods: A quantitative analysis was performed to evaluate the number of ocular medications with a paediatric license in Italy, the UK, and the USA. A literature search was also performed in MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs) on ophthalmic pharmacological therapy in children aged < 18 years, published up to December 2010. A search in the international clinical trial registries, the list of paediatric investigation plans (PIPs) approved by European Medicines Agency (EMA), and the table of medicines with new paediatric information approved by Food and Drug Administration (FDA) was also performed.

Results: In all, of 197 drugs identified, 68 (35%) single drugs are licensed for paediatric use at least in one considered country, while 23 (12%) were marketed in all three countries. More specifically, in Italy 43 single drugs (48% of those marketed) had a paediatric license, while 39 (64%) did in the UK and 22 (54%) did in the USA. Only 13 drugs were marketed with a paediatric license in all countries.

The percentage of drugs licensed for paediatric use and for which at least one RCT had been performed ranged between 51% in Italy and 55% in the USA. No published RCTs were found for 11 (48%) drugs licensed for paediatric use in all three countries. In all, 74 (35%) of the retrieved RCTs involved mydriatic/cycloplegic medications.

A total of 62 RCTs (56% completed) on 46 drugs were found in the international clinical trial registries. Cyclosporin and bevacizumab were being studied in many ongoing trials. Twenty-six drugs had new paediatric information approved by FDA based on new paediatric clinical trials, while only 4 PIPs were approved by EMA.

Conclusions: There is a pressing need for further research and clinical development in the pediatric ophthalmic area, where effective up-to-date treatments, and additional research and education on use in children, remain priorities.

Keywords: review, ocular medicines, eye diseases, drug therapy, paediatrics

Background

Many drugs on the market labelled for adult use contain no information on paediatric use because their safety and efficacy have not been well studied in paediatric patients [1]. Many widely used drugs therefore include disclaimers stating that the paediatric use is “not recommended”.

Despite the prevalence of eye disease in early childhood (in the United Kingdom, by 3 years of age 5.7% of children had had ≥ 1 eye condition, 0.24% of which associated with visual impairment) [2] more than in other paediatric areas, evidence for the rational use of ocular medicines in these patients is very scant.

Many ocular medications are used in children to treat common bacterial and viral infections, inflammation and allergy, uveitis and glaucoma, as well as other conditions...
including myopia, amblyopia, and strabismus [3], even if data regarding their safety and effectiveness in the paediatric population are sparse. In 2000, a review of the 98 most commonly used or prescribed topical ophthalmic drugs found that only 51% provided information on paediatric use [4]. Without adequate paediatric labelling information, practitioners treating eye disease in children may be forced to prescribe ocular medications in an “off-label” manner, placing their paediatric patients at risk for serious adverse reactions [5,6].

Children are not small adults. Statements regarding paediatric drug use must be age-specific to indicate for which group a drug has been studied: newborns, infants, pre-school children, school-age children, and adolescents. These groups differ not only in size and body weight but in physiology and metabolism as well [7]. Children, in particular infants and neonates who have thin eye membranes, may be particularly vulnerable to systemic effects of topical ophthalmic drugs as the doses used are often not weight-adjusted and are similar to doses used in adults. Systemic absorption may have a greater impact in children than in adults due to their lower body mass, altered metabolic capacity, and an immature blood brain barrier, leading to potentially higher plasma levels for a longer period of time and to a much greater risk of serious systemic side effects [8].

In addition to these differences, other characteristics unique to the paediatric population include the lack of commercially available dosage forms and concentrations appropriate for paediatric patients and the lack of published research on the pharmacokinetics and clinical use of new drugs [9]. The result is the high frequency of serious medication errors.

A study was planned to compare the availability and the licensing status of ocular medications marketed in Italy, the United Kingdom (UK), and the United States of America (USA) related to the amount of published and un-published RCTs testing these drugs in the paediatric population.

Methods

Ocular medications were identified and classified according to the International Anatomical-Therapeutical-Chemical classification system (ATC) [10] as S01: antibiotics, antivirals, anti-allergy drugs, non-steroidal anti-inflammatory drugs (NSAIDs), steroids, diagnostic agents, lubricants, glaucoma medications, local anaesthetics, and vascular endothelial growth factor inhibitors (anti-VEGF drugs) and combinations. A quantitative analysis was performed to record the number of ophthalmic drugs available on the market and those approved for paediatric use in Italy, the UK, and USA. Data on the licensing status of individual drugs were obtained by consulting national formularies: Italy’s Repertorio Farmaceutico Italiano (Refi) [11], the UK’s British National Formulary (BNF) [12], and the USA’s Physicians’ Desk Reference® (PDR®) [13].

In order to collect randomized controlled trials (RCTs) on safety and efficacy of ophthalmic drugs in the paediatric population, a bibliographic search for ophthalmological therapy in children aged up to 18 years in the MEDLINE (1967 - December 2010), EMBASE (1975 - December 2010), and Cochrane Central Register of Controlled Trials (1967 - December 2010) databases was performed. The MeSH search terms and additional keywords used in the search strategy were: child/infant/newborn/adolescent, ophthalmology, drug therapy, and randomized controlled trials, limiting the results to human. To make the search more complete, the terms were searched for both in the database dictionaries and through the free text search option that covered the articles’ titles and abstracts. All the references retrieved were collected and analyzed using the software program Reference Manager, version 11 (Institute for Scientific Information, Berkeley, California). The titles and abstracts were screened independently by two reviewers (FF and AC) to assess the relevance of the studies. Contrasting results were reviewed by a third person (MB).

We also searched for guidelines concerning paediatric ophthalmology management in MEDLINE and EMBASE, in the National Guidance Clearinghouse, National Library of Guidelines Specialist Library, National Institute for Clinical Excellence (NICE), Australian National Health and Medical Research Council, Canadian Medical Association InfoBase and New Zealand Guidelines Group databases, and on the American Academy of Pediatrics, Canadian Pediatric Society, and Royal College of Pediatrics websites.

In addition, a search for paediatric clinical trials on ocular medications in the World Health Organization’s International Clinical Trials Registry Platform (ICTRP) [14], the ClinicalTrials.gov registry [15], and the International Standard Randomized Controlled Trial Number Register (ISRCTN) [16] was performed in order to find which of these drugs are under paediatric investigation. Furthermore, the list of paediatric investigation plans (PIPs) approved by EMA [17], the “List of the active substances included in the work-sharing procedure in accordance with Articles 45 and 46 of the European Paediatric Regulation” [18], and the FDA’s “Table of Medicines with new paediatric information”, a list of drugs approved for paediatric use resulting from the paediatric clinical trials performed in response to paediatric legislative initiatives [19], and the updated priority list for studies into off-patent paediatric medicinal products [20], were also consulted in order to assess if there is a gap between research and clinical practice.
Results

Quantitative analysis
A total of 197 ocular medications were reported in the 2010 ATC index, respectively, 88 (45%), 63 (31%), and 41 (21%) of which were marketed in Italy, the UK, and the USA.

In all, 68 (35%) single drugs are licensed for paediatric use in at least one considered country, while 23 drugs (12%) were marketed in all three countries. More specifically, in Italy 43 single drugs (48% of those marketed) had a paediatric license, while 39 (64%) did in the UK and 22 (54%) did in the USA. Only 13 drugs were marketed with a paediatric license in all the countries (Table 1). Only 3 licensed drugs appear in the World Health Organization (WHO) list of paediatric essential drugs. Tetracycline as 1% eye ointment and adrenaline as 2% eye drops, considered essential drugs for children, were not licensed for paediatric use in any country.

Fifteen single drugs and six combinations (mainly anti-infective, anti-inflammatory, and anti-allergy medications) were licensed for paediatric use only in Italy, while 16 single drugs and 8 combinations were licensed only in the UK (mainly local anaesthetics and lubricants), and 2 single drugs and 8 combinations only in the USA (mainly anti-infective medications). Almost all anti-infective medications and combinations had a paediatric license in all three countries, while no local anaesthetics are licensed for paediatric use in Italy and USA and no NSAIDs are in the UK.

Wide differences were found in the age groups for which the drugs were licensed and only for 6 drugs the age range is the same or similar in all countries.

Qualitative analysis

Bibliographic search
The bibliographic search produced 158 RCTs on 69 single drugs and combinations, involving a total of 18,816 children (Table 2). The percentage of drugs licensed for paediatric use with at least one RCT ranged between 51% in Italy and 55% in the USA. No published RCTs were found for 11 (48%) ocular medications licensed for paediatric use in all three countries.

In all, 74 retrieved RCTs (35%) regarded mydriatic/cycloplegic medications, mainly antimuscarinic agents. In particular, 31 RCTs involving 3,530 children belonging to all age groups studied atropine as eye drops 1%, a drug licensed for paediatric use only in the UK (≥3 months). In addition, 3 studies were available on pirenzepine, a drug not licensed for paediatric use in any country.

Regarding the treatment of allergic conjunctivitis, 49 (23%) RCTs on 11 drugs were found: 22 studies involved 6 anti-histamine agents (azelastine, bepotastine, emedastine, ketotifen, levocabastine, and olopatadine) tested in children ≥3 years, and 9 RCTs involved 3 mast cell stabilizers, such as lodoxamide, cromoglicate, and nedocromil, in children ≥4 years. Bepotastine is the only drug unlicensed for paediatric use in all considered countries.

A total of 43 RCTs (21%) concerned 20 antibacterial agents and their combinations, 8 of them (40%) not licensed for paediatric use in any country considered, such as the fluoroquinolone besifloxacin as eye suspension 2%, tested in 3 RCTs in children older than one year. Among the six combinations studied 3 were licensed for paediatric use in the UK and 2 in the USA, while none in Italy. In addition, the anti-infective agent povidone-iodine, licensed for use in children older than 1 month, was studied only in Italy in 3 RCTs.

Among the medications commonly used in ophthalmic surgical procedures (e.g. strabismus surgery) there were 7 local anaesthetics (proparacaine, not licensed for paediatric use in any country was the drug most studied), 3 steroids (dexamethasone, fluorometholone, and rimexolone), and 3 NSAIDs (diclofenac, ketorolac, and flurbiprofen).

Ten RCTs regarded anti-glaucoma agents: 7 were on 3 beta-blockers, 2 on carbonic anhydrase inhibitors, and the last one on an acetylcholinesterase inhibitor, echothophate iodide. The most studied drug is timolol, a beta-blocker licensed for use in children older than 1 month only in Italy, as well as the carbonic anhydrase inhibitor dorzolamide.

Phenylephrine, the only decongestant agent studied, licensed for paediatric use in all countries considered, was involved in 11 RCTs, in which it was used in combination with a mydriatic/cycloplegic agent for eye examinations in children. In one RCT involving 10 neonates, phenylephrine was used alone.

Guidelines

Eight guidelines on pharmacological management of eye diseases in children were found: they addressed acute bacterial conjunctivitis [21], amblyopia [22,23], strabismus [24], glaucoma [25], retinopathy of prematurity (ROP) [26,27], and prophylaxis of neonatal ophthalmia [28] (Table 3). Those concerning screening methods for diagnosing eye diseases in the paediatric population without drug use were not reported.

Five guidelines (2 regarding ROP, 2 regarding amblyopia, and 1 regarding strabismus) recommended drug use only for screening or post-surgical therapy, and not for the pharmacological management of the disease in childhood.

Almost all of the drugs listed in the guidelines are not licensed for use in children in any country considered, especially for prophylaxis of neonatal ophthalmia (no drug licensed), for the medical management of childhood glaucoma (5 out of 8 drugs are unlicensed) and acute bacterial conjunctivitis (8 out of 22 drugs are unlicensed).
| Pharmaco-therapeutic Group | Drug name                  | Licence Status | RCTs | IT  | UK  | USA | Published | Non-published |
|----------------------------|----------------------------|----------------|------|-----|-----|-----|-----------|--------------|
| ANTI-ALLERGY MEDICATIONS   |                            |                |      |     |     |     |           |              |
| Anti-histamine agent       | Azelastine                 | ≥ 4 yrs        | ≥ 12 yrs | ≥ 3 yrs | 4 | -   |            |              |
|                            | Emedastine                 | ≥ 3 yrs        | ≥ 3 yrs | ≥ 3 yrs | 1 | -   |            |              |
|                            | Epinastine                 | ≥ 12 yrs       | ≥ 12 yrs | ≥ 3 yrs | - | -   |            |              |
|                            | Ketotifen                  | ≥ 3 yrs        | ≥ 3 yrs | ≥ 3 yrs | 5 | 3   |            |              |
|                            | Levocabastine              | all            | NA    | NA    | 6 | -   |            |              |
|                            | Olopatadine                | ≥ 3 yrs        | ≥ 3 yrs | ≥ 3 yrs | 4 | 1   |            |              |
| Mast cell stabilizer       | Spaglumic acid             | all            | NA    | NA    | - | -   |            |              |
|                            | Lodoxamide                | all            | ≥ 4 yrs | ≥ 2 yrs | 1 | -   |            |              |
|                            | Nedocromil sodium          | ≥ 6 yrs        | ≥ 6 yrs | ≥ 3 yrs | 5 | -   |            |              |
|                            | Sodium cromoglicate        | ns**           | all    | NA    | 6 | -   |            |              |
|                            | Pemirolast                 | NA             | NA    | ≥ 3 yrs | - | -   |            |              |
| Decongestant (Sympathomimetic agent) | Naphazoline | ≥ 10 yrs | NA | nl | - | 1 | | |
|                            | Oxymetazoline              | ≥ 3 yrs        | NA    | ≥ 6 yrs | - | -   |            |              |
|                            | Tetryzoline                | ≥ 3 yrs        | NA    | ≥ 6 yrs | - | -   |            |              |
| ANTI-ALLERGY COMBINATIONS  |                            |                |      |     |     |     |           |              |
| Anti-histamine agent + Decongestant | Antazoline + Xylometazoline | NA | ≥ 5 yrs | NA | - | - | | |
|                            | Chlorpheniramine + Tetryzoline | ≥ 3 yrs | NA | NA | - | - | | |
|                            | Pheniramine + Tetryzoline  | ≥ 3 yrs        | NA    | NA    | - | -   |            |              |
| Mast cell stabilizer + Decongestant | Cromoglicate + Tetryzoline | ≥ 3 yrs | NA | NA | - | - | | |
| Astringent + Decogestant   | Zinc sulfate + Tetryzoline | NA             | NA    | ≥ 6 yrs | - | -   |            |              |
| Decogestant + Lubricants   | Tetryzoline + Povidone + Dextran 70 + Polyethylene glycol 400 | NA | NA | ≥ 6 yrs | - | - | | |
| ANTI-GLAUCOMA MEDICATIONS  |                            |                |      |     |     |     |           |              |
| Beta-blocker               | Timolol                    | > 1 m          | nl**  | nl   | 4 | 2   |            |              |
| Carbonic anhydrase inhibitor | Dorzolamide               | all            | nl    | ns   | - | -   |            |              |
| Sympathomimetic agent (selective α2 - agonist) | Apraclonidine | ≥ 12 yrs | ≥ 12 yrs | nl | - | - | | |
|                            | Brimonidine                | ≥ 12 yrs       | NA    | ≥ 2 yrs | - | 1   |            |              |
|                            | Clonidine                  | ns             | NA    | NA    | - | -   |            |              |
| Parasympathomimetic (colinergic) agent | Aceclidine | ≥ 3 yrs | NA | NA | - | - | | |
|                            | Pilocarpine                | ≥ 3 yrs        | nl    | Nil   | - | -   |            |              |
| ANTI-GLAUCOMA COMBINATIONS |                            |                |      |     |     |     |           |              |
| Beta-blocker + Carbonic anhydrase inhibitor | Timolol + Dorzolamide | ≥ 2 yrs | nl | ≥ 2 yrs | 1 | - | | |
| Beta-blocker + Sympathomimetic agent | Timolol + Brimonidine | nl | NA | ≥ 2 yrs | - | - | | |
| ANTI-INFLAMMATORY MEDICATIONS |                        |                |      |     |     |     |           |              |
| Non-Steroidal Anti-Inflammatory Drug (NSAID) | Diclofenac | ≥ 3 yrs | nl | nl | 4 | 1 | | |
|                            | Indomethacin               | ≥ 3 yrs        | NA    | NA    | - | -   |            |              |
|                            | Ketorolac                  | NA             | nl    | ≥ 3 yrs | 3 | -   |            |              |
| Steroid agent              | Betamethasone              | NA             | all   | NA    | - | -   |            |              |
|                            | Desonide                   | > 1 m          | NA    | NA    | - | -   |            |              |
|                            | Dexamethasone              | > 1 m          | all   | nl    | 6 | 2   |            |              |
|                            | Fluorometholone            | ≥ 2 yrs        | ≥ 2 yrs | ≥ 2 yrs | 3 | 1   |            |              |
Table 1 Paediatric licensing status and number of RCTs related to ocular medications (Continued)

| Steroid agent + Decongestant | Hydrocortisone | Prednisolone | Clobetasone | Fluorometholone + Tetryzoline | Clobetasone + Tetryzoline | Neomycin + Tetryzoline |
|-------------------------------|----------------|--------------|-------------|-------------------------------|--------------------------|------------------------|
|                               | > 1 m all      | NA all nl   | > 1 m NA NA | ≥ 2 yrs NA NA                | NS NA NA                | ≥ 1 yr NA nl  |
| ANTI-INFECTIVE MEDICATIONS   | 21/13 9/9 10/7 | 27 3        |             |                               |                          |                        |
| Antibacterial agent           | Chloramphenicol | ≥ 3 yrs all | NA 7       |                               |                          |                        |
| Aminoglycoside                | Gentamycin     | ≥ 3 yrs all | > 1yr 2    |                               |                          |                        |
|                                | Neomycin       | NA all NA   | -           |                               |                          |                        |
|                                | Netilmicin     | > 1 m NA NA | -           |                               |                          |                        |
|                                | Tobramycin     | ≥ 1 yr NA nl| 3           |                               |                          |                        |
| Quinolone                     | Ciproflaxacin  | all ≥ 1 yr  | ≥ 1 yr 2    |                               |                          |                        |
|                               | Gatifloxacin   | NA NA 1 yr | -           |                               |                          |                        |
|                                | Levofloxacin   | ≥ 1 yr ≥ 1yr | ≥ 1 yr 2  |                               |                          |                        |
|                                | Lomefloxacin   | ≥ 1 yr NA NA| -           |                               |                          |                        |
|                                | Moxifloxacin   | ≥ 1 m nl ≥ 1yr 3 |          |                               |                          |                        |
|                                | Ofloxacin      | nl ophtalmia| > 1m ≥ 1yr 1 |                               |                          |                        |
| Antiviral agent                | Acyclovir      | all all nl  | -           |                               |                          |                        |
| Other anti-infective agent     | Idoxuridine    | ≥ 3 yrs NA | NA -       |                               |                          |                        |
|                                | Trifluridine   | ≥ 6 yrs NA | 4 2        |                               |                          |                        |
| ANTIBACTERIAL COMBINATIONS     | 9/2 6/3 4/1 3 | 0           |            |                               |                          |                        |
| Antibacterial                  | Polimyxin B + Trimethoprim | NA all > 2 yrs 1 |          |                               |                          |                        |
|                                | Polimyxin B + Bacitracin    | NA all nl 1 |           |                               |                          |                        |
|                                | Neomycin + Polymyxin B + Gramicidin | NA ≥ 2 yrs nl |          |                               |                          |                        |
|                                | Neomycin + Chloramphenicol | ns NA NA | -       |                               |                          |                        |
| Antibacterial + Steroid        | Neomycin + Polymyxin B + Dexamethasone | nl all ≥ 2 yrs - |          |                               |                          |                        |
|                                | Neomycin + Polymyxin B + Hydrocortisone | NA NA ns | -       |                               |                          |                        |
|                                | Neomycin + Chloramphenicol + Hydrocortisone | ns NA NA | -       |                               |                          |                        |
|                                | Neomycin + Predisolone | ns all NA | -       |                               |                          |                        |
|                                | Neomycin + Fluocinolone | ns NA NA | -       |                               |                          |                        |
|                                | Neomycin + Betamethasone | NA all NA 1 |          |                               |                          |                        |
|                                | Tobramycin + Dexamethasone | nl NA ≥ 2 yrs |          |                               |                          |                        |
|                                | Prednisolone + Sulphacetamide | NA NA ≥ 6 yrs |          |                               |                          |                        |
|                                | Tobramycin + Fluometholone | NA NA ≥ 2 yrs |          |                               |                          |                        |
| Antibacterial + Steroid + Decongestant | Neomycin + Gramicidin + Tetryzoline + Dexamethasone | ≥ 3 yrs NA NA | -  |                               |                          |                        |
The authors indicated that all these drugs are generally used in a off label manner and that the majority of data on these medications are from adult studies.

Finally, no guidelines on the pharmacological treatment of allergic conjunctivitis were found.

Search for the paediatric RCTs in registries

A search performed in the World Health Organization’s International Clinical Trials Registry Platform (ICTRP), the ClinicalTrials.gov registry, and the International Standard Randomized Controlled Trial Number Register (ISRCTN) found 46 ocular medications currently under paediatric investigation in 62 RCTs (56% of which completed). Cyclosporin, an immunosuppressant agent, and bevacizumab, a humanized monoclonal antibody, were the drugs involved in the most studies: 7 RCTs testing cyclosporine in the treatment of keratoconjunctivitis (4),

### Table 1 Paediatric licensing status and number of RCTs related to ocular medications (Continued)

| MYDRIATIC/CYCLOPLEGIC MEDICATIONS | ≥ 2 yrs | 6/5 | 2/1 | 55 | 3 |
|----------------------------------|--------|-----|-----|----|---|
| Antimuscarinic agent             | Cyclopentolate | ≥ 3 yrs | > 3 ms | all | 14 |
|                                  | Homatropine   | ns   | > 3 ms | nl  | -  |
|                                  | Tropicamide   | > 1 m | all    | NA  | 10 |
|                                  | Atropine      | ns   | > 3 ms (nl ≥ 6 yrs) | NA  | 31 |
|                                  | Ibopamine     | all  | NA    | NA  | -  |
| Decongestant (Sympathomimetic agent) | Phenylephrine | ≥ 12 yrs | All (nl 10% drops) | NA  | 2  |
| PERI-OPERATIVE MEDICATIONS       | Lidocaine     | nl   | all   | nl  | 2  |
|                                  | Oxybuprocaine | ns   | all   | NA  | 1  |
|                                  | Proxymetacaine| NA   | all   | NA  | -  |
|                                  | Tetracaine    | NA   | all   | NA  | 1  |
| LUBRICANTS AND ASTRINGENTS       | Polyvinyl alcohol | Ns | all   | NA  | -  |
|                                  | Carmellose sodium | ns | all   | NA  | -  |
|                                  | Hydroxyethylcellulose | NA | all   | NA  | -  |
|                                  | Paraffin      | NA   | all   | NA  | -  |
|                                  | Sodium hyaluronate | ns | all   | NA  | -  |
|                                  | Hypermellose  | NA   | all   | nl  | -  |
| LUBRICANT COMBINATIONS           | Hypermellose + Glycerin | NA | NA   | all | -  |
|                                  | Hypermellose + Dextran 70 | NA | all   | nl  | -  |
|                                  | Hypermellose + Glycerin + Polyethylene glycol 400 | NA | NA   | ≥ 6 yrs | -  |

| OTHER OCULAR MEDICATIONS         | Hypertonic agent | Sodium chloride | NA | all | NI  | -  |
|                                  | Ocular diagnostic agent | Fluorescein | ns | all | NA  | -  |
|                                  | Topical immunomodulator | Cyclosporine 0.05% | NA | NA | ≥ 16 yrs | -  |
|                                  | Other ocular agent | Heparin | ≥ 1 m | NA | NA  | -  |
| TOTAL SINGLE DRUGS               | 68 | 88/43 | 61/39 | 41/22 | 140 | 20 |
| TOTAL COMBINATIONS               | 29 | 16/7 | 10/6 | 14/7 | 4 | - |

Note: Only drugs with a paediatric licence at least in one country are listed. The drugs in bold are listed in the WHO model list of essential medicines for children.

* N° drugs marketed/N° drugs marketed with paediatric licence
** ns: not specified; nl: not licensed for paediatric use; NA: not authorised
Table 2 Summary of retrieved RCTs on the use of ocular medications in the paediatric population

| Pharmaco-therapeutic Group                  | Drug name                        | Formulation                  | N° RCTs | N° Children | Age range |
|--------------------------------------------|----------------------------------|------------------------------|---------|-------------|-----------|
| MYDRIATIC/CYCLOPLEGIC MEDICATIONS          |                                  |                              | 74 (35%)|             |           |
| Antimuscarinic agent                       | Atropine                         | eye drops 1%                 | 31      | 3530        | all       |
|                                           | Cyclopentolate                    | eye drops 0.5%               | 2       | 28          | ≤ 13 yrs  |
|                                           |                                  | eye drops 1%                 | 11      | 181         | ≤ 16 yrs  |
|                                           | Tropicamide                       | eye drops 1%                 | 9       | 348         | all       |
|                                           | Pirenzepine                       | ophthalmic gel 1%           | 3       | 276         | 6 - 12 yrs|
|                                           | Cyclopentolate/Tropicamide        | eye drops 1%/1%              | 6       | 176         | all       |
| Sympathomimetic agent                     | Phenylephrine                     | eye drops 2.5%              | 1       | 10          | ≤ 1 m     |
| Antimuscarinic agent + Sympathomimetic agent | Tropicamide/Phenylephrine      | eye drops 1%/2.5%            | 3       | 92          | ≤ 1 m     |
|                                           |                                  | eye drops 0.5%/2.5%          | 2       | 51          | ≤ 8 yrs   |
|                                           |                                  | eye drops 0.5%/0.5%          | 1       | 12          | 3-11 yrs  |
|                                           | Cyclopentolate/Phenylephrine     | eye drops 1%/2.5%            | 2       | 30          | ≤ 6 yrs   |
|                                           |                                  | eye drops 0.2%/1%            | 3       | 99          | ≤ 1 m     |
| ANTI-INFECTIVE MEDICATIONS                |                                  |                              | 51 (24%)|             |           |
| Antibacterial agent                       | Chloramphenicol                   | eye drops 0.5%              | 7       | 1664        | ≤ 12 yrs  |
|                                           | Azithromycin                      | eye drops 1%                 | 1       | 335         | ≥ 1 yr    |
|                                           |                                  | eye drops 1.5%               | 2       | 542         | ≥ 1 yr    |
|                                           | Tetracycline                      | eye drops 1%                 | 2       | 518         | 1- 10 yrs |
|                                           |                                  | eye ointment 1%              | 2       | 218         | ≥ 6 ms    |
|                                           | Besifloxacin                      | eye suspension 0.6%          | 3       | 1124        | ≥ 1yr     |
|                                           | Fusidic acid                      | eye drops 1%                 | 3       | 594         | ≤ 2 yrs   |
|                                           | Moxifloxacin                      | eye drops 0.5%               | 3       | 645         | all       |
|                                           | Tobramycin                        | eye drops 3%                 | 3       | 741         | ≤ 12 yrs  |
|                                           | Ciprofloxacin                     | eye drops 0.3%               | 2       | 193         | ≤ 12 yrs  |
|                                           | Levofloxacin                      | eye drops 0.5%               | 2       | 106         | 1-16 yrs  |
|                                           | Gentamycin                        | eye ointment 1%              | 2       | 117         | ≤ 12 yrs  |
|                                           | Erythromycin                      | eye drops 1%                 | 1       | 110         | ≤ 1 m     |
|                                           |                                  | eye ointment                 | 1       | 24          | ≤ 1 yr    |
|                                           | Ofloxacin                         | eye drops 0.3%               | 1       | 23          | ≥ 2 yrs   |
|                                           | Oxytetracycline                   | eye drops 1%                 | 1       | 450         | ≤ 1 m     |
|                                           | Sulphacetamide                    | eye drops 10%                | 1       | 14          | ≤ 1 m     |
| Antibiotics combinations                  | Polymyxin B/Oxytetracycline       | eye ointment 1%              | 2       | 132         | 2-10 yrs  |
|                                           | Polymyxin B/Bacitracin            | eye ointment 1%              | 1       | 66          | ≥ 1 m     |
|                                           | Polymyxin B/Trimethoprim          | eye drops 1%                 | 1       | 28          | all       |
| Antibacterial agent + NSAID               | Gentamycin/Diclofenac             | eye drops                  | 1       | 12          | ≤ 12 yrs  |
| Antibacterial agent + Steroid agent       | Neomycin/Betamethasone            | eye drops                  | 1       | 12          | ≤ 12 yrs  |
|                                           | Tobramycin/Dexamethasone          | eye drops                  | 1       | 28          | 4-10 yrs  |
| Antifungal agents                         | Miconazole                        | eye suspension 1%           | 1       | 12          | ≥ 15 yr   |
|                                           | Econazole/Miconazole              | eye suspension 1%/1%        | 1       | 7           | ≥ 15 yr   |
| Other anti-infective eye preparation      | Povidone-iodine                   | eye drops 2.5%              | 4       | 3132        | ≤ 1 yr    |
|                                           | Silver nitrate                    | eye drops 1%                | 1       | 450         | ≤ 1 m     |
| ANTI-ALLERGY MEDICATIONS                  |                                  |                              | 31 (15%)|             |           |
Table 2 Summary of retrieved RCTs on the use of ocular medications in the paediatric population (Continued)

| Anti-histamine agent | Medication | Route | Age | Count |
|----------------------|------------|-------|-----|-------|
| Levocabastine        | eye suspension 0.5% | 6 | 174 | ≥ 3 yrs |
| Ketotifen            | eye drops 0.025% | 5 | 522 | ≥ 3 yrs |
| Olopatadine          | eye drops 0.2% | 4 | 99  | ≥ 3 yrs |
| Azelastine           | eye drops 0.02% | 4 | 132 | ≥ 4 yrs |
| Beopotastine         | eye drops 1% | 1 | 60  | ≥ 10 yrs |
|                      | eye drops 1.5% | 1 | 36  | ≥ 10 yrs |
| Emedastine           | eye drops 0.05% | 1 | -   | 3-16 yrs |

| Mast cell stabilizer | Medication | Route | Age | Count |
|----------------------|------------|-------|-----|-------|
| Lodoxamide          | eye drops 0.1% | 1 | 15  | ≥ 6 yrs |
| Cromoglycate        | eye drops 2% | 3 | 128 | ≥ 4 yrs |
|                      | eye drops 4% | 1 | 30  | ≥ 16 yrs |
| Nedocromil          | eye drops 2% | 3 | 85  | ≥ 4 yrs |

| ANTI-INFLAMMATORY MEDICATIONS | 18 (9%) |
|-----------------------------|--------|
| Corticosteroid              | 6 |
| Dexamethasone               | eye drops 0.1% | 6 | 159 | all |
| Fluorometholone             | eye drops 0.1% | 3 | 52  | ≤ 10 yrs |
| Rimeoxolone                 | eye drops 1% | 1 | 22  | 4-8 yrs |

| NSAID                       | 3 |
| Diclofenac                  | eye drops 0.1% | 4 | 93  | ≥ 2 yrs |
| Ketorolac                   | eye drops 0.5% | 3 | 70  | ≤ 12 yrs |
| Flurbiprofen                | eye drops | 1 | 50  | ≥ 5 yrs |

| ANTIGLAUCOMA MEDICATIONS | 10 (5%) |
|-------------------------|--------|
| Beta-blocker            | 2 |
| Timolol                 | eye drops 0.25% | 2 | 44  | 7-13 yrs |
|                         | eye drops 0.5% | 1 | 12  | ≥ 14 yrs |
|                         | gel-forming solution 0.25% | 1 | 35  | ≤ 6 yrs |
|                         | gel-forming solution 0.5% | 1 | 36  | ≤ 6 yrs |
| Betaxolol               | eye suspension 0.25% | 1 | 52  | ≤ 6 yrs |
| Levobetaxolol           | eye suspension 0.5% | 1 | 46  | ≤ 6 yrs |
| Carbonic anhydrase inhibitor | 1 |
| Brinzolamide            | eye suspension 1% | 1 | 32  | ≤ 6 yrs |
| Dorzolamide             | eye drops 2% | 1 | 56  | ≤ 6 yrs |

| Acetylcholinesterase inhibitor | 2 |
| Echophosphate iodide | eye drops | 1 | 20  | - |

| PERI-OPERATIVE MEDICATIONS | 18 (9%) |
|---------------------------|--------|
| Local anaesthetic agent   | 2 |
| Bupivacaine               | subconjuntival infiltration | 2 | 38  | 5-10 yrs |
|                         | eye drops 0.5% | 1 | 17  | 3-6 yrs |
| Proparacaine              | eye drops 0.5% | 3 | 58  | ≤ 1 m |
| Lidocaine                 | eye drops 2% | 1 | 10  | 3-14 yrs |
|                         | ophthalmic gel 2% | 1 | 24  | 3-12 yrs |
| Amethocaine               | eye drops 0.5% | 2 | 45  | 2-8 yrs |
| Levobupivacaine           | eye drops | 1 | 13  | 1-16 yrs |
| Oxybuprocanine            | eye drops 0.4% | 1 | 20  | 3-8 yrs |
| Tetracaine                | eye drops 1% | 1 | 44  | 1-12 yrs |
| Sucrose                   | eye drops | 1 | 11  | ≤ 1 m |

| Chemotherapeutic agents    | 2 |
| Mitomycin C               | eye drops 0.02% | 1 | 10  | ≥ 6 yrs |
|                         | oculair injection 0.4% | 1 | 7   | ≥ 6 yrs |
| S-fluorouracil           | oculair injection | 1 | 4   | ≤ 12 yrs |
| Mitomycin C/S-fluorouracil | oculair injection | 1 | 4   | ≤ 12 yrs |

| OTHER DRUGS | 7 (3%) |
|-------------|-------|
| Vernal keratoconjunctivitis | 2 |
| Cyclosporine | eye drops 2% | 1 | 14  | 5-16 yrs |
|               | eye drops 1.25% | 1 | 20  | 5-14 yrs |
|               | eye drops 1% | 1 | 32  | 5-14 yrs |
### Table 2 Summary of retrieved RCTs on the use of ocular medications in the paediatric population (Continued)

| Treatment                              | Disease                  | Quality of evidence | Country | Year |
|----------------------------------------|--------------------------|---------------------|---------|------|
| Mipragoside ophthalmic gel 0.5%        |                          |                     |         |      |
| ROP therapy                            | Bevacizumab intravitreal injection |                     |         |      |
| Esotropia                              | Botulinum toxin ocular injection |                     |         |      |
| Dacryocystitis                         | Herba houttuyniae eye drops |                     |         |      |
| TOTAL (69 single drugs & combinations) |                          |                     | 209     | 18,816|

NOTE: the total is higher than the sum of the RCTs (158) because some drugs were tested in more than one trial. The references to RCTs are available upon request to the corresponding author.

### Table 3 Summary of guidelines on pharmacological therapy of ocular disease in the paediatric population

| Ref. | Organisation                      | Title                                                                 | Disease                  | Quality of evidence | Treatment (Licensing status)                                                                 | Country | Year |
|------|-----------------------------------|-----------------------------------------------------------------------|--------------------------|---------------------|-----------------------------------------------------------------------------------------------|---------|------|
| [41] | National Guideline Clearinghouse (NGC) | Guidelines for the treatment and management of acute bacterial conjunctivitis in children and adults. | Acute bacterial conjunctivitis | I                   | Topical antibiotic therapy.                                                                 | USA     | 2005 |
|      |                                   |                                                                       |                          |                     | • Norfloxacin 0.3% (nl)                                                                         |         |      |
|      |                                   |                                                                       |                          |                     | • Ciprofloxacin 0.3%                                                                          |         |      |
|      |                                   |                                                                       |                          |                     | • Ofloxacin 0.3%                                                                               |         |      |
|      |                                   |                                                                       |                          |                     | • Levofloxacin 0.5% (nl UK, nl USA)                                                             |         |      |
|      |                                   |                                                                       |                          |                     | • Lomefloxacin 0.3%                                                                           |         |      |
|      |                                   |                                                                       |                          |                     | • Moxifloxacin 0.5% (nl UK)                                                                    |         |      |
|      |                                   |                                                                       |                          |                     | • Gatifloxacin 0.3% (nl IT, nl UK)                                                              |         |      |
|      |                                   |                                                                       |                          |                     | • Chloramphenicol 0.5% (nl USA)                                                                 |         |      |
|      |                                   |                                                                       |                          |                     | • Sulfacetamide Sodium 10% (nl)                                                                 |         |      |
|      |                                   |                                                                       |                          |                     | • Erythromycin 0.5%                                                                            |         |      |
|      |                                   |                                                                       |                          |                     | • Gentamicin Sulfate 0.3%                                                                      |         |      |
|      |                                   |                                                                       |                          |                     | • Tobramycin Sulfate/Polymyxin B 10000 U/1mg/mL (nl IT)                                        |         |      |
|      |                                   |                                                                       |                          |                     | • Fusidic acid 0.1% (nl IT, nl USA)                                                             |         |      |
|      |                                   |                                                                       |                          |                     | • Tobramycin 0.3% (nl UK, nl USA)                                                               |         |      |
|      |                                   |                                                                       |                          |                     | • Povidone-iodine 1.25% (nl UK, nl USA)                                                          |         |      |
|      |                                   |                                                                       |                          |                     | • Bacitracin (nl)                                                                               |         |      |
|      |                                   |                                                                       |                          |                     | Ocular steroids and steroid-antibiotic:                                                        |         |      |
|      |                                   |                                                                       |                          |                     | • Prednisolone (nl IT, nl USA)                                                                  |         |      |
|      |                                   |                                                                       |                          |                     | • Flurometholone 0.1%/sulfacetamide sodium 10% (nl)                                            |         |      |
|      |                                   |                                                                       |                          |                     | • Flurometholone 0.1%                                                                          |         |      |
|      |                                   |                                                                       |                          |                     | • Neomycin/polyoxymin B/dexamethasone 0.1% (nl IT)                                             |         |      |
|      |                                   |                                                                       |                          |                     | • Gentamicin 0.3%/prednisolone acetate 0.1% (nl)                                               |         |      |
|      |                                   |                                                                       |                          |                     | • Tobramycin 0.3%/dexamethasone 0.1% (nl)                                                       |         |      |
|      |                                   |                                                                       |                          |                     | • Silver nitrate 1% eye drops (nl)                                                              | Canada  | 2002 |
|      |                                   |                                                                       |                          |                     | • Erythromycin 0.5% ointment (nl)                                                               | (Rev.   | 2009 |
|      |                                   |                                                                       |                          |                     | • Tetracycline 1% ointment (nl)                                                                 |         |      |
| [34] | Canadian Paediatric Society       | Recommendations for the prevention of neonatal ophthalmia             | Prophylaxis to prevent neonatal ophthalmia due to N gonorrhoeae | III                  | • B-Blockers: Betaxolol 0.25% (nl)                                                             | UK      | 2007 |
|      |                                   |                                                                       |                          |                     | • Carbonic Anhydrase Inhibitors: Dorzolamide 2% (nl UK, nl USA)                                |         |      |
|      |                                   |                                                                       |                          |                     | • Prostaglandin Analogs: Latanoprost (nl), Travoprost (nl), Bimatoprost (nl)                    |         |      |
|      |                                   |                                                                       |                          |                     | • Adrenoceptor Agonists: Brimonidine (nl UK), Apraclonidine (nl)                                |         |      |
|      |                                   |                                                                       |                          |                     | • Parasympathomimetics: Pilocarpine (nl UK, nl USA)                                             |         |      |
|      |                                   |                                                                       |                          |                     | • Refractive correction (glasses)                                                               |         |      |
|      |                                   |                                                                       |                          |                     | • Patching: from 2 to 6 hours per day                                                            |         |      |
|      |                                   |                                                                       |                          |                     | • Atropine (nl IT, nl USA)                                                                      |         |      |
| [29] | Moore W. and Nischal K.K.          | Pharmacologic management of glaucoma in childhood                      | Glaucma                  | I                   |                                                                                               |         |      |
| [39] | Royal College of Ophthalmologists  | Guidelines for the management of amblyopia                            | Ambliopia                | III                  |                                                                                               |         |      |

[For full references and sources, please refer to the original document or the authors listed in the tables.]
dry eye syndrome (2), and pterygia (1), and 4 RCTs on bevacizumab in the treatment of neovascular glaucoma in children > 3 years (all 3 completed) and in ROP in neonates > 5 months (1 ongoing RCT).

Among the drugs that had the most ongoing studies were also two anti-histamine drugs, ketotifen and bepotastine, and the antibacterial moxifloxacin: these were tested in 3 RCTs each for the treatment of allergic or bacterial conjunctivitis in children.

EMA/FDA viewpoint

Although no ophthalmologic drugs are found in the EMA’s priority list for studies into off-patent paediatric medicinal products at this time, the EMA Paediatric Committee (PDCO) adopted opinions on PIPs for 12 ocular medications, with the aim to generate the necessary quality, safety, and efficacy data to support the authorization of these medicines for use in children.

Four drugs, cysteamine, latanoprost, voclosporin and the recombinant human monoclonal antibody to human interleukin 17A received a go-ahead for a PIP, while one, travoprost/brinzolamide, was refused it. In four cases, one involving the anti-inflammatory agent bromfenac, one a new drug, ocplasmin, for the treatment of symptomatic focal vitreomacular adhesion, and two the vascular endothelial growth factor inhibitors, ranizumab and pegaptanib, a waiver was granted in all age groups on the grounds that the specific medicinal product does not represent a significant therapeutic benefit or because the disease or condition for which the product is intended does not occur in the specified paediatric subset(s). Finally, 2 steroid drugs, dexamethasone and triamcinolone, were refused the granting of a product-specific waiver on the grounds that the clinical studies cannot fulfil a therapeutic need of the paediatric population.

By consulting the “List of the active substances included in the work-sharing procedure in accordance with Articles 45 and 46 of the European Paediatric Regulation, no additional data or information on their use in the paediatric population resulted to be submitted or requested to authorise the paediatric use of any ocular medicinal product.

Twenty-six ocular medications were found in the Food and Drug Administration (FDA)’s “Table of Medicines with New Paediatric Information”, a list of drugs approved for use in the paediatric population resulting from the paediatric clinical trials performed in response to paediatric legislative initiatives. Ten (38%) were anti-allergy medications, 8 (31%) were anti-glaucoma medications (6 of which were not yet licensed for paediatric use in the USA), and 5 were antibacterial and combinations. The last three agents were triamcinolone (steroid agent), lidocaine (local anaesthetic agent), and a hypromellose combination (lubricant). These drugs included approved information on use in the paediatric population resulting from the paediatric clinical trials performed in response to paediatric legislative initiatives.

Discussion

This article reviews ocular medication use in children, providing a summary of their licensing status in Italy, the UK, and the USA and analyse the amount of available studies testing these medicines in the paediatric population. Most of the drugs listed have only recently obtained paediatric use approval and are now widely prescribed for children by a growing number of clinicians [29]. However, for most of these drugs wide differences in the licensed age groups were found and only a few are available in all three countries. Even if the Paediatric Regulation in EU and USA specifically aims at giving children the same access to authorised medicinal products suitable for their use, the age approval and occasionally the approach towards certain therapeutic problems is under
the direct responsibility of National Authorities, so differences in drug licensing procedure between countries remain. There is therefore a need for evidence-based harmonization of drug licenses in order to guarantee equal drug availability and access [30].

Furthermore, many ocular medications commonly used in children still do not have paediatric dosing and safety labelling information in any country. For example, almost for all glaucoma medications (such as prostaglandin analogues and carbonic anhydrase inhibitors), paediatric use is labelled “not recommended”.

At this time no paediatric RCTs were available for several ocular medications. When available, the studies were often limited to small case series and case reports, so more extensive controlled trials will be needed to confirm their safety and efficacy also in paediatric population. On the contrary, evidence on efficacy was found for drugs that were not licensed for children, such as tetracycline and bupivacaine.

In spite of the fact that no ophthalmologic drugs are found in the EMA’s priority list, several drugs were recently studied in paediatric clinical trials in the European countries and the USA. In particular, the ongoing research is examining the potential use of intravitreally injected anti-VEGF drugs, such as bevacizumab, successfully used in adults with diabetic retinopathy or age-related macular degeneration (AMD), a cause of a severe vision loss among the aging population in many western countries [31,32]. These drugs could now also be used in paediatric vitreoretinal diseases, as shown by recent studies on intravitreal injection of bevacizumab for the treatment of ROP, the leading cause of childhood blindness [33-37].

Moreover, the available guidelines on the pharmacological management of eye diseases in the paediatric population often recommend the use of medications not licensed or investigated in children, especially for the management of glaucoma (such as prostaglandin analogs) or acute bacterial conjunctivitis (such as steroids and antibiotics combinations). An effort to stimulate research and clinical development is therefore needed also for them, in order to guarantee medicines that have been proven to be of benefit also in paediatric patients.

Many good ethical and economical reasons exist for limiting paediatric clinical trials, while guaranteeing appropriate conclusions. Because of the characteristics of the paediatric population, limited information is also available regarding the side effects related to ocular medication use in children [38]. As the number and variety of ocular medications has increased and the number of clinicians involved in their prescription has grown, the risk of systemic adverse reactions may also increase [39,40]. When prescribing ocular medications in children, physicians should therefore carefully consider their risk/benefit profile, referring to details of labelling for paediatric use, such as the age of the child for whom the drug is approved, and be aware of their potentially serious systemic side effects [5].

Some strategies for reducing systemic absorption and toxicity should be followed whenever possible. First of all, the lowest available dosage of medication necessary to achieve a therapeutic benefit while minimizing risk should be used. Secondly, since different formulations may have different degrees of systemic absorption, formulations with lower systemic absorption, which may be more suitable for use in children, should be used. Ophthalmic gel or ointment, for example, has been found to have reduced systemic absorption compared to the ophthalmic solution [28]. In addition, paediatric patients should be monitored closely during and after treatment for local and systemic side effects [29].

The present findings suggest that access to, and rational use of, ocular medications in the paediatric population continue to present a considerable challenge. Paediatric clinical trials are important for defining how infants and children respond to medications and for identifying age-specific toxic effects [41]. While recent legal and economic incentives in both Europe and the USA stimulate research to obtain more data regarding dosing, efficacy, and safety of medicines used in children, problems remain in obtaining adequate evidence [42]. In this context, there is a pressing need for further clinical research to improve the quality, efficacy, and safety of ocular medications offered to paediatric patients. Clinical research must be carried out using appropriate methodologies (e.g. study design, sample size, randomization, and blinding) [38] also (and in particular) in the paediatric ophthalmic area, where effective up-to-date treatments, and additional research and education on use in children, remain priorities [43].

Conclusion

European and American legislation has established that children should have the same rights as adults to receive medicines that have been proven to be of benefit and that are unlikely to cause serious toxicity [44]. Even if the legislative initiatives in both Europe and the USA emphasize the importance of large clinical trial in children, prioritizing the medicines to be studied on the basis of children’s needs [45], differences between countries in drug licensing procedures, and occasionally in the approach towards certain therapeutic problems, may be quite significant [30]. A formulary containing common “paediatric” evidence-based safety and efficacy information could be a useful tool for improving the rational use of drugs in children and adolescents, harmonizing inter-country drug regulations and availability [46].

In addition, recommendations from high quality RCTs and systematic reviews, and effective knowledge translation
strategies are essential to clinicians and policy makers in planning changes in practice that could ultimately improve patient- and system-related outcomes. All such considerations are priorities for an area, such as ophthalmic drug therapy in children, that is lacking evidence.

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FF carried out the bibliographical search, screened studies for inclusion, performed data extraction and analysis, and drafted the manuscript; AC provided methodological advice; MB participated in the design of the study and revised the manuscript. All authors read and approved the final manuscript.

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