

ORIGINAL ARTICLE

Use and reimbursement of off-label drugs in pediatric anesthesia: the Italian experience

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Summary

Background: Most of the drugs used in anesthesia are off-label in children even if they present solid clinical evidence in adults. This lack of authorization is caused by multiple factors including the difficulty in conducting research in this area (due to the ethical concerns and/or the low number of available participants, the high variability of the outcome measures) and the lack of economic interest of the pharmaceutical companies (due to the limited market).

Objective: Define a list of medicinal products commonly used off-label in pediatric anesthesia to be reimbursed by Italian National Health System.

Methods and results: We hereby describe the methodological framework used to allow reimbursed use of a list of medicinal products, widely used off-label in pediatric patients, ensuring the best therapeutic results with the lowest possible risk for children. A task force of pediatric anesthesiologists from Italy petitioned the Italian Medicines Agency (AIFA) to allow a number of commonly utilized but off-label drugs for pediatric anesthesia to be reimbursed for specific indications. For each drug, both the supporting literature and expert opinion were used, and the resulting list of drugs allowed to be used/reimbursed officially by AIFA was significantly expanded. This paper documents one approach to the problem of off-label use of drugs for pediatric patients that can be a model for future efforts.

Conclusion: Continuous efforts are needed from government institutions and sponsors on drug development and on drug approval process in pediatrics, as research on drug effectiveness and safety is mandatory in children as in adults. At the same time, clinicians must become more familiar with the drug-approval process, participate to sponsored trials, and perform trials themselves.

Introduction

Off-label use of medicinal products in children is common in current medical practice. A look into the historical context helps to elucidate the framework for the use of medicines in children. Proper labeling of medicinal products is a relatively recent innovation. In 1950, a US court case established that the directions for use on a product label must include the product purpose. A further step was taken in 1962, when US legislation

required manufacturers to prove not only the safety but also the efficacy of drugs by adequate clinical trials. Between 1962 and 1965, most European countries promulgated similar legislations, in the wake of the thalidomide disaster (1).

Since then, the pharmaceutical knowledge has progressed fast, but most of the evidence on the efficacy and safety of drugs concerns adult population. The discrepancy between the availability of medicines for adults and that for children is starting to be

considered. Therefore, many countries are seeking to improve knowledge about safety and efficacy of drugs used in pediatric patients, that is, patients from birth to <18 years of age.

Indications, doses, and route(s) of administration of many medical products have been established for adults. However, unlicensed or off-label use in children of many active pharmaceutical ingredients is common and sometimes inevitable. Yet, this practice can be dangerous (2), because the particular pharmacokinetic and pharmacodynamic behavior of children may lead to unexpected adverse effects. Specific characteristics are difficult to study and may be different from those observed in adults.

Experiments conducted on young animals have shown that the administration of anesthetic drugs can induce apoptosis in some cells, especially neurons, and a progressive disorganization of cell membranes (3,4). Another study has shown that approximately 50% of the medicinal products used in children are off-label or unlicensed, and about 70% of pediatric patients receive at least one prescription under these conditions (5). These products are used in children even if their efficacy and/or safety is demonstrated only in adults, because there is no authorized valid alternative.

In August 2012, the Italian Medicines Agency (AIFA – Agenzia Italiana del Farmaco) issued a list of drugs that are fully refundable by Italian National Health System (NHS) for specific and established, but off-label indication. This list includes medicinal products belonging to several pediatric therapeutic areas, including anesthesia, and products for use in adults. This resolution was approved in the context of Italian Law 648/1996, which states that AIFA can make a list of drugs, whose off-label or unlicensed use is at the expense of Italian NHS if ‘there is no therapeutic alternative’.

Italian NHS does not directly refund medications for use within hospitals; therefore, the interest of this list in pediatric anesthesia, which is obviously performed almost exclusively within hospitals, responds more to scientific and cultural needs and, possibly, legal aspects, rather than to a financial requirement. As a matter of fact, this list directs clinicians to choose the most appropriate medication when marketing authorization is absent and regulatory evidence is insufficient.

Here, we describe the work behind the publication of this list, which was based on expert opinion and literature data. The methodological framework was recently designed to respond more effectively to the needs of AIFA, trying to ensure the best therapeutic results and the lower possible risks for the pediatric patients.

Methods

A group of anesthesiologists (Appendix S1) in charge of pediatric anesthesia and intensive care in several Italian children hospitals and general hospitals with huge pediatric departments, including one of the authors, wrote a letter to AIFA suggesting a list of drugs to be authorized. The document was endorsed by four Italian anesthesia scientific societies (Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care [SIAART-I], Italian Society of Neonatal and Paediatric Anaesthesia and Resuscitation [SARNePI], Italian Association of Cardiothoracic Anaesthesiologist [ITACTA], Italian Resuscitation Council [IRC]). The request urged AIFA to update the list of drugs, whose off-label use in pediatric population is refundable by the Italian NHS.

Most of anesthetic agents, not licensed for pediatric use, are used in clinical practice and believed to be sufficiently safe and effective. In Italy, the off-label use of drugs is allowed under certain conditions, and its possible reimbursement by the Italian NHS is regulated by the law 648/1996.

For the purposes of this article, pediatric population ranged from birth to puberty and was divided into three groups: neonates (age: 0–4 weeks), infants (age: <1 year), and children (age: from 1 to 17 years).

The list of suggested drugs to be authorized included active ingredients used in the majority of the Italian children hospitals and general hospitals with huge pediatric departments considered essential for clinical practice and to solve at least in part this difficult situation. The list contained new and old anesthetic and analgesic drugs. The further selection of the drugs performed by the Technical Scientific Committee of AIFA was based on expert opinion and critical analysis of the scientific literature. The work lasted almost 2 years and involved a comparison between the pediatric indications recognized by AIFA and included in Italian pediatric formularies [Pagine Sanitarie (6) and Guida all’uso dei farmaci (7)], those recognized by the British National Formulary (2010–11 edition) (8), a critical analysis of the literature (summarized in Appendix S2) and indications of guidelines published by scientific societies [EPLS (9) and APA (10)]. A systematic approach was not possible due to the lack of evidence concerning the use of these drugs in pediatric population. The aim was to identify at least one drug for each specific indication and for each age group, and the widest diffuse products were preferred, according to the principle of ‘established by use’. The list included new pediatric indications for drugs who already had an adult indication and off-label use of medicaments who were already approved for children for other indications. The final draft was reviewed by

the Pediatric Working Group and the Clinical Trials Office of AIFA (Appendix S3), and finally approved and published on August 27, 2012 (11).

Results

Italian Medicines Agency now lists 12 anesthetic medicines that are refundable by Italian NHS for specified off-label use (Table 1). All these medicines are licensed in Italy for adult use, and no experimental or unlicensed medicine is present. Three widely used anesthetic drugs (thiopental, ketamine, and nitrous oxide) had no pediatric on-label indication. For the other nine medications (sevoflurane, diazepam, dantrolene sodium, morphine, ibuprofen, ketorolac, lidocaine + prilocaine, codeine, and atropine), this document allows reimbursed use in other age groups, other indications (two cases), or with different routes of administration. Diazepam is now reimbursed also for premedication before general anesthesia and atropine can be prescribed as an antimuscarinic agent and to treat intraoperative bradycardia.

Further drugs of anesthesiological interest, such as anticoagulants and analgesic drugs, had been published by AIFA following similar pathways and are reported in Table 2. Anticoagulant medications (enoxaparin, sodium heparin, and warfarin) had no previous pediatric indication. Oxycodone and tramadol were not licensed for pediatric use, but now off-label use from 1 month and from 12 years old, respectively, are reimbursed.

Table 3 reports the anesthesiological drugs whose indication was considered already adequate by AIFA experts.

Discussion

Proper drug labeling is a relatively new process. It emerged half a century ago when the U. S. legislation forced manufacturers to prove the safety and efficacy of drugs by adequate clinical trials. Nowadays, competent authorities [European Medicines Agency (EMA) or National Drug Agencies] evaluate the trials carried out by the pharmaceutical industry and decide the extent to which the manufacturer will be allowed to market the new drug.

Most of the drugs used in anesthesia and intensive care are off-label in children, even if they present solid clinical evidence in adults, because studies in children are rarely conducted by the pharmaceutical companies or by the academic investigators. This lack of authorization is caused by many factors, including the great difficulty of conducting research in this area. The main reasons are ethical concerns, size and variability of the samples, and lack of economic interest of the

pharmaceutical companies. Furthermore, clinicians generally start using new agents in children only after years of experience in adult population. Clinical trials have become very expensive, involving hundreds to thousands of patients and millions euros of budget. Many older drugs such as thiopental, ketamine, and fentanyl are generic and cheap, therefore marketing authorization holders have little or no interest in performing trials to reach approval and labeling in the pediatric setting. As a consequence, most of the drugs needed to perform anesthesia are not approved for pediatric use.

National Drug Agencies try to encourage on-label use of drugs in pediatric population throughout economic incentives for conducting pediatric studies. In 1997, U. S. Food and Drug Administration (FDA) established the pediatric exclusivity provision, which provides 6 months of exclusivity to be attached to any existing exclusivity or patent protection on a drug for which FDA has requested pediatric studies and where the manufacturer has conducted such studies in accordance with the requirements of FDA. A similar strategy was adopted by the EMA with the introduction of the Pediatric Use Marketing Authorizations (PUMAs) within the Pediatric Regulation. This type of marketing authorization covers the indication and appropriate formulation for the pediatric population. A PUMA will benefit from 10 years of market protection as a reward for the development in children. The first (and so far only) to obtain the PUMA is midazolam (Buccolam), to treat prolonged epileptic seizure in children aged 3 months or older.

Off-label prescription of medicines in Italy must be done under the direct responsibility of the treating physician and requires the collection of explicit informed consent for each drug, according to Italian Law 94/1998, article 3.

Later on, Italian legislation also set reimbursement restrictions for off-label drugs: they are not reimbursed by the Italian NHS outside clinical trials, if there is an on-label therapeutic alternative ('Finance Act 2007', Law 296/2006, article 1, paragraph 796, letter z).

Despite legal restrictions, off-label prescription is a diffuse practice in pediatrics. Most data come from the US, where approximately 80% of all approved pharmaceuticals do not include labeling for children (12), about 50% of the drugs used in children are off-label, and in about 70% of pediatric patients, at least one drug is prescribed under these conditions (3). Premature and newborn children are almost always excluded from drug trials because of their differences in metabolic pathways, and immature hepatic and renal function (13).

Some encouraging data come from the 'five-year report to the European Commission' on the experience

Table 1 List of the anesthetic drugs that are fully refundable by Italian National Health System and their specific new off-label authorization^a

	Previous pediatric indication in Italy	New pediatric off-label authorization in Italy
Intravenous anesthetic drugs		
Thiopental	None	General anesthesia induction starting from birth
Ketamine	None	Induction and maintenance of general anesthesia (from birth) and premedication (from 1 month of life) through im, rectal, or iv (bolus and continuous infusion) administration
Inhalatory anesthetic drugs		
Sevoflurane	Induction and maintenance of general anesthesia (from 1 month of life)	Induction and maintenance of general anesthesia starting ;from birth
Nitrous oxide (N ₂ O)	None	Mild anesthetic or analgesic drug (from birth). Maintenance of general anesthesia in association with other drugs
Sedative and anxiolytic drugs		
Diazepam	MICROPAM: treatment of seizures (including febrile seizures). Sedation for diagnostic or operative procedures. NOAN: Treatment of insomnia and of somatic or psychiatric symptoms associated with anxiety disorder (only when the psychiatric disorder is severe and extremely disabling)	Premedication through oral or iv administration (from 1 month of life)
Analgesic drugs		
Morphine	Premedication through im administration (from 1 year of life). Treatment of acute pain through sc, im, or iv (from birth). Treatment of chronic through oral administration (from 1 year of life). Sedation in ICU	Treatment of pain through oral or rectal (from 1 month of life). Adjuvant analgesic drug through epidural administration (from 1 year of life)
Ibuprofen	Treatment of fever and acute pain through oral administration (from 3 months of life or in children weighing more than 5 kg)	Treatment of pain, hyperpyrexia, and inflammation through oral administration (from 1 month of life)
Ketorolac	Treatment of acute postoperative pain (from 16 years of life)	Treatment of acute pain through oral or im administration (from 16 years of life), and through iv administration (from 6 months of life)
Local anesthetic drugs		
Lidocaine + Prilocaine	Minor interventions such as venipuncture or minor surgery (i.e., circumcision) through topical administration (from 1 month of life)	Topical administration from birth (preterm neonates excluded)
Miscellanea		
Codeine	Treatment of pain through oral administration (from 1 year of life)	Treatment of pain through oral, sc, rectal, or im administration (from birth)
Atropine	Premedication through iv, sc, and im administration (from 1 year of life). Not authorized as antimuscarinic agent and for treatment of intraoperative bradycardia	Premedication through oral, sc, and iv administration (from birth). As antimuscarinic agent and for treatment of intraoperative bradycardia (from birth)
Dantrolene sodium	Treatment of malignant hyperthermia	Treatment of malignant hyperthermia from 1 month of life

im, intramuscular; iv, intravenous; sc, subcutaneous.

^aTable summarized and translated from 'Supplement P3 – AIFA Resolution of August 27, 2012'.

Table 2 List of the drugs of anesthesiological interest that will be fully refundable by Italian National Health System and their new specific off-label authorization. These drugs were listed among treatments for hematological, neurological, and musculoskeletal pathologies^a

	Previous pediatric indication in Italy	New pediatric off-label authorization in Italy
Anticoagulant drugs		
Enoxaparin	None	Prophylaxis and treatment of deep venous thrombosis and pulmonary embolism, even CVC-related, through sc or iv administration. Therapy of arterial thrombosis. Prophylaxis of extracorporeal coagulation in hemodialysis and hemofiltration
Sodium heparin	None	Prophylaxis and treatment of venous and arterial thrombosis. Prophylaxis of central and peripheral venous catheter occlusion and related thrombosis
Warfarin	None	Secondary prevention of deep venous thrombosis and pulmonary embolism
Analgesic drugs		
Fentanyl	Long-term treatment of chronic pain (from 2 years of life, already treated with opioids), through td administration	Treatment of procedural pain and postoperative pain (from birth). Sedation during mechanical ventilation (from birth). Epidural analgesia (from birth)
Oxycodone	None	Treatment of moderate to severe pain
Tramadol	None. Contramal© drops is authorized from 1 year of life. The other formulations of Contramal© are authorized from 12 years of life	Treatment of moderate to severe pain and of postoperative pain
Diclofenac	Rheumatic diseases with articular (rheumatoid arthritis, osteoarthritis) and extra-articular (peri-arthritis, bursitis, tendonitis, myositis, and sciatica) manifestations. Post-traumatic flogosis and edema from 14 years of life	Treatment of juvenile idiopathic arthritis (from 6 months of age). Treatment of postoperative pain, through oral or rectal administration
Indomethacin	None	Closure of patent arterial duct in preterm neonates

CVC, central venous catheter; iv, intravenous; sc, subcutaneous; td, transdermal.

^aTable summarized and translated from 'Supplement P5–P8 – AIFA Resolution of August 27, 2012'.

acquired as a result of the application of the Pediatric Regulation, prepared by the EMA with its Pediatric Committee (14). From 2005 to 2011, the proportion of pediatric trials among all trials increased from 7.6 to 9.9%. In 2006, no preterm newborns or newborns were enrolled in clinical trials, and a total of 2190 children were enrolled in clinical trials, while in 2011, 3341 newborns and a total of 22 563 children were enrolled (14).

Some concerns involve specifically the pediatric anesthesiologist as some animal studies show that anesthetic drugs may lead to neuron apoptosis and progressive cell membrane disorganization in developing individuals (3,4). This aspect is particularly difficult to be detected in human observational studies, because neonates that need anesthesia often have severe comorbidities due to prematurity (15).

Italian Medicines Agency was able to approve a first list of off-label drugs to be reimbursed in the perioperative period according to the provisions of Italian Law 648/1996, which can apply to off-label drugs for which, 'there is no therapeutic alternative' and those so-called drugs 'established by use'. This list was published on the

'Official Gazette of the Italian Republic' on August 27, 2012 and took legal effect the day after. Hospital pharmacies were actively informed of this determination by AIFA, so that they could communicate to the hospital physicians and update their drug storage.

This first important result has been achieved thanks to the cooperation and efforts of the Italian Children Hospitals, Anesthesia Scientific Societies (SIAARTI; SARNePI; ITACTA; IRC), and the Clinical Trials Office of AIFA.

Limitations

The list of drugs suggested by the pediatric anesthesia and intensive care specialists also included lorazepam, neostigmine, and levobupivacaine, but these drugs had an unauthorized alternative and were therefore not included in the list of off-label drugs to be reimbursed in the perioperative period. Furthermore, there are several drugs used in pediatric intensive care units that have not been addressed in the process, and some drugs (e.g., atropine) might have been included with an archaic

Table 3 List of the anesthetic drugs that were considered to have adequate on-label authorization and their specific indication

	Pediatric indication in Italy
Intravenous anesthetic drugs	
Propofol	Induction and maintenance of general anesthesia, from 1 month to 3 years of life only 1% formulation. Induction and maintenance of general anesthesia from 3 years of life, any formulation
Midazolam	Conscious sedation for diagnostic or therapeutic procedures (from 6 months of life). Sedation in intensive care (from birth). Premedication before general anesthesia (from 6 months of life). Treatment of prolonged seizures (from 3 months of life)
Inhalatory anesthetic drugs	
Desflurane	Maintenance of general anesthesia (from birth)
Isoflurane	Maintenance of general anesthesia (from 2 years of life)
Analgesic drugs	
Alfentanil	Induction and maintenance of general anesthesia (from birth)
Remifentanil	As an analgesic drug, for induction and maintenance of general anesthesia (from 1 year of life)
Acetaminophen	Antipyretic and analgesic drug (from birth)
Neuromuscular blocking drugs	
Atracurium	Induction and maintenance of general anesthesia (from 1 month of life)
Cisatracurium	Induction of general anesthesia (from 1 month of life). Maintenance of general anesthesia through repeated boluses or continuous infusion (from 2 years of life)
Mivacurium	Induction and maintenance of general anesthesia (from 2 months of life)
Pancuronium	Induction and maintenance of general anesthesia (from birth)
Rocuronium	Induction and maintenance of general anesthesia (from 1 month of life). Continuous infusion administration allowed
Vecuronium	Induction and maintenance of general anesthesia (from birth)
Suxamethonium	Induction and maintenance of general anesthesia through im and iv administration (from birth)
Local anesthetic drugs	
Lidocaine	Local anesthesia (from birth)
Bupivacaine	Local and regional anesthesia (from 1 year of life)
Ropivacaine	Regional anesthesia through epidural or caudal administration (from birth)
Miscellanea	
Sugammadex	Reversal of neuromuscular blockade by rocuronium and vecuronium (from 2 years old)
Naloxone	Counter the effects of opiate overdose (from birth)
Flumazenil	Counteract the sedative effects of benzodiazepines (from 1 year of life)

im, intramuscular; iv, intravenous.

indication (e.g., premedication). A systematic approach was not used and probably was not possible due to the lack of evidence concerning the use of these drugs in pediatric population; even if the process was carried out by several experts, this could have brought to pitfalls in selection. Clinicians are crucial to urge drug agencies to add new drugs and indications, according to the clinical challenges they meet in everyday practice either in the anesthesiology or in the intensive care settings. Another important limitation is that most new/expanded indications do not include newborns. As this was the first time that such a process was carried on for pediatric anesthesia, it was decided to choose a prudent approach that leads to often exclude newborns from the new authorized indications. As few data concerning this age group

are available and all procedures in these patients are life-saving, clinicians can give the medication based on their knowledge and experience. This list does not provide the scientific evidence of the effectiveness and safety of these drugs in pediatric setting. Nevertheless, it allows clinicians to enlarge their toolbox in the field of anesthesia, sedation, and perioperative management, so that they can operate within the law more easily.

Conclusion

We described the organizational methodology that allowed reimbursing the use of several anesthetics and analgesics in the pediatric setting with benefits for clinicians and patients. Continuous efforts are needed from

government institutions and sponsors on drug development and on drug approval process in pediatrics, as research on drug effectiveness and safety is mandatory in children as in adults. At the same time, clinicians must become more familiar with the drug-approval process, participate to sponsored trials, and perform investigator-based trials themselves. Off-label use cannot be recommended as a general rule and remains a measure to be adopted only if necessary to address urgent clinical needs. However, when using off-label drugs, clinicians must develop recommendations for pharmacotherapy, and report new experiences and side effects that can help give supportive data to the agency for the final evaluation. European Pediatric Regulation (Appendix S4) should be taken into consideration.

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Conflict of interest

All authors have no conflicts of interest to disclose.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 The anesthesiologists in charge of pediatric anesthesia and intensive care in several Italian children hospitals and general hospitals with huge pediatric departments who wrote a letter to AIFA suggesting a list of anesthetics drugs to be authorized in children.

Appendix S2 List of the literature published by the ‘Official Gazette of the Italian Republic’ on August 27, 2012.

Appendix S3 Members of the Pediatric Working Group and the Clinical Trials Office of the Italian Medicines Agency (AIFA – Agenzia Italiana del Farmaco).

Appendix S4 Regulation of the European Parliament and of the Council (EC) No 1901/2006.

Appendix 1.

The anesthesiologists in charge of pediatric anesthesia and intensive care in several Italian children hospitals and general hospitals with huge pediatric departments who wrote a letter to AIFA suggesting a list of anesthetics drugs to be authorized in children.

Ida Salvo, MD	Children H. Buzzi, Milan
Edoardo Calderini, MD	University H. Policlinico, Milan
Giorgio Conti, MD	University H. S. Cuore, Rome
Raffaella Pagni, MD	Children H. Salesi, Ancona
Pietro Tuo, MD	Children H. Gaslini, Genoa
Simonetta Baroncini, MD	University H. S. Orsola Malpighi, Bologna
Giorgio Ivani, MD	Children H. Regina Margherita, Turin
Silvana Molinaro, MD	Children H. Riuniti, Brescia
Andrea Messeri, MD	Children H. Meyer, Florence
Fabio Borrometi, MD	Children H. Santobono, Naples
Marinella Astuto, MD	General H. Vittorio Emanuele, Catania
Stefano Furlan, MD	Children H. Burlo Garofalo, Trieste
Dario Salvo, MD	General H. S. Vincenzo, Taormina
Sergio Picardo, MD	Children H. Bambino Gesù, Rome

Appendix 2.

List of literature published by the "Official Gazette of the Italian Republic" on the 27 of august 2012

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Appendix 3

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Appendix 4.

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL (EC) No 1901/2006

Article 45

1. By 26 January 2008, any pediatric studies already completed, by the date of entry into force, in respect of products authorized in the Community shall be submitted by the marketing authorisation holder for assessment to the competent authority. The competent authority may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned. The Agency shall coordinate the exchange of information (omissis)

Article 46

1. Any other marketing authorisation holder-sponsored studies which involve the use in the pediatric population of a medicinal product covered by a marketing authorisation, whether or not they are conducted in compliance with an agreed pediatric investigation plan, shall be submitted to the competent authority within six months of completion of the studies concerned. 2. Paragraph 1 shall apply independent of whether or not the marketing authorisation holder intends to apply for a marketing authorisation of a pediatric indication.

3. The competent authority may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly.

4. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

5. The Agency shall coordinate the exchange of information.