Evolution of paediatric off-label use after new significant medicines become available for adults: a study on triptans in Finnish children 1994–2007

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Off-label use in children is widespread. New medicines lack marketing authorization for paediatric use, even when they represent significant therapeutic advantages and are intended for treatment of conditions common in children.
- Until now no information exists on how off-label use in children develops over time after a significant new medicine is approved for adults and what happens when it is later labelled for one paediatric age group.

WHAT THIS STUDY ADDS

- Off-label use of a new significant medicine begins in adolescents and extends to younger children with delay. First marketing authorization to adolescents, providing a more child-friendly formulation, results in increase of off-label use in younger children, and has limited effect on total off-label use.

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AIM

To investigate the evolution of paediatric off-label use after a therapeutically new group of medicines for a common condition becomes available for adults but is labelled for children with a delay of several years.

METHODS

Triptans were used as a model, because migraine is common in children, and is the only indication for triptans. Data on all triptan prescriptions 1994–2007 were extracted from the nationwide Finnish Prescription Register. Prescriptions for children were compared over time.

RESULTS

Paediatric patients with triptan prescriptions increased from 204 in 1994 to 2618 in 2007. Sumatriptan accounted for 64% of all paediatric triptan prescriptions. When sumatriptan in a nasal formulation was labelled for children ≥ 12 years in 2003, off-label prescribing to younger children (6–11 years) doubled in 2003–2004. Sumatriptan on-label prescriptions increased to 728 adolescents (45% of sumatriptan in the age group) in 2007, but its off-label use continued also to increase to 1119 (61% of paediatric sumatriptan prescriptions) in 2007. In that year 72% of paediatric triptan use was off-label, 28% on-label.

CONCLUSIONS

When a new significant medicine becomes available in adults, off-label use in children starts slowly but continues to extend to younger children reaching a market size which is little influenced by late appearance of a labelled product. Paediatric treatment remains dominated by off-label use despite labelling of a product in an age appropriate formulation to the most relevant age group.

Introduction

New therapeutically significant medicines are usually approved for treatment of adults and lack marketing authorization for paediatric use even when intended for treatment of diseases also common in children [1]. Extension of authorization to cover use in children is typically delayed, sometimes with good justification [2]. The consequence is off-label use in children, which can be widespread [3–5].

Regulatory and legislative incentives are currently offered to pharmaceutical companies in Europe and USA for new paediatric data and labelling of medicines for children. On the other hand it has been suggested that off-label use might weaken the interest of pharmaceutical companies to conduct costly trials and apply for marketing authorization if a product has already widely penetrated the market [6]. The extent and problems of off-label and unlicensed use of medicines in children are well documented [7–9]. The effects of a later paediatric labelling and age-appropriate formulations (dosage forms) on the extent of off-label and on-label use would be of high interest. Unfortunately, longitudinal studies on the dynamics and development of off-label use in children are lacking.

The first triptan, sumatriptan, was launched in 1991. Since then, six other triptans (naratriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan and frovatriptan) have entered the market. The first triptan labelled in the paediatric age group was sumatriptan, when a 10 mg/dose nasal spray was approved for adolescents in the age group of 12–17 years, first in Australia in 2002.

To investigate how off-label and on-label use of a new, significant class of medicines developed, we conducted a nationwide longitudinal study on triptan use in the paediatric population in Finland in 1994–2007. Triptans were chosen as a model, migraine being common in the paediatric age group (3–7% of children and 10% of adolescents suffer from migraine) and migraine being the exclusive indication for triptans [10, 11].

Methods

In Finland, public health insurance covers reimbursements on the patients' costs of medicines prescribed in outpatient care in the public system (health centres), by occupational health care and in private practice [12, 13]. Expenditure funds are financed by employer and employee contributions and the state. The reimbursement system is managed by the Social Insurance Institution (SII) and covers all permanent residents in Finland (5.3 million in 2007). A unique social security number identifies each insured person and expresses the day of birth and gender of the insured. All purchases of reimbursable medicines are recorded in a computerized National Prescription Register managed by the SII. For persons having an additional

private insurance, the majority of medicine purchases are first compensated by the direct state reimbursement in a pharmacy, thereby being included in the register. In the years 1994–2007 the register covered 97% of all reimbursed purchases. Medicines used in hospitals or sold over-the-counter are not included in the register.

As triptans fall into the basic reimbursement category (health insurance finances 42% of the drug cost and patient co-payments cover 58%), the purchases of triptans are recorded in the Prescription Register. The register was set up in 1994, leaving the first 18 months of triptan use outside this study.

All pharmacy-dispensed triptan purchases during the years 1994–2007 were extracted from the register. Different triptans were classified according to the Anatomical Therapeutic Chemical (ATC) classification, the fifth level [14]. Altogether 110 products belonged to reimbursable drugs during the study period, representing all triptan products on market in Finland (Pharmaceuticals Pricing Board, Reimbursable triptans, personal communication). The date of receiving marketing authorization and admission of reimbursement of each drug was determined from official sources (Pharmaceuticals Pricing Board, Reimbursable triptans, personal communication) [15].

The triptan use each year was measured by the number of individuals having received reimbursement for a triptan. One person could have several triptan purchases during 1 year as each prescription authorizes a maximum duration of 1 year treatment and a reimbursed medication can be dispensed for no longer than 3 months at a time. The dispense date of the medication and the unique identity number (social security number) means that the age of a person at the moment of purchase can be defined. For this study the age of a person using a triptan was defined based on his/her first purchase each year.

Migraine is rare in children younger than 6 years [11, 16], which was confirmed as only 43 children 0–5 years old got reimbursement for a triptan during 1994–2007 (representing on average 0.26% of all children prescribed a triptan each year). These small children are also difficult to dose appropriately with adult formulations, so we excluded children younger than 6 years from the study, and thus our final data include the age range of 6–17 years. The study population was divided in two subgroups, children 6–11 years old and adolescents 12–17 years old, as sumatriptan, the only triptan labelled during the study period in this age range, was labelled for children above the age of 12 years.

Triptan use was classified as off-label if the age of a person prescribed a triptan deviated from the age recommendations given in the Summary of Product Characteristics valid in Finland [17]. Other forms of off-label prescribing, like deviations in dosing, could not be analyzed from the data available. Data on children 6–17 years getting reimbursement for a sumatriptan nasal spray 10 mg/dose (paediatric) or 20 mg/dose (adult) formulation

were additionally extracted separately in order for a closer examination of the use of the paediatric formulation once it became available (in Finland in 2003).

Retrospective, descriptive analysis was conducted as frequency distributions. The number and proportion of persons prescribed a triptan in different age groups was compared over time with respect to drug, age, gender and additionally to migraine prevalence data from the literature [10, 11].

Ethical considerations

To protect confidentiality, the data were analyzed on a patient group level and the personal identity codes were not included in the final data.

Results

The first triptan, sumatriptan, came to the market in Finland in 1992. The launch of the other six triptans (naratriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan and frovatriptan) is presented in Table 1. The first triptan labelled in the paediatric age group, sumatriptan in a 10 mg/dose nasal spray, received marketing authorization in Finland at the end of 2003. In 2010, 18 years after the launch of the first sumatriptan for adults, it is still the only triptan labelled in Finland in the age group below 18 years.

Total use of the triptans in children and adolescents

In all, 19 599 children and adolescents were reimbursed for a triptan for either on- or off-label use during the

years 1994–2007. The majority of the adolescents (age 12–17 years) were girls (70%). In children (age 6–11 years) boys used a triptan slightly more often (53%) than girls. The annual number of paediatric patients prescribed a triptan increased from 204 in year 1994 to 2 618 in year 2007, a thirteen-fold increase (Figure 1). The largest annual growth (39%) occurred from 2003 to 2004, when sumatriptan was labelled for the above 12-year age group and became available in an age appropriate formulation.

Sumatriptan has kept its position as the most commonly prescribed triptan, accounting for 64% of the paediatric prescriptions. After the launch of other triptans, starting in 1998, the growth of sumatriptan off-label use levelled, but started to grow again after labelling for adolescents at the end of 2003. Of the newer triptans, zolmitriptan (14.6% of total paediatric use) and rizatriptan (11.1%) were most widely used by children and adolescents.

Triptan use in relation to the population suffering from migraine

The number of adolescents aged 12–17 years in Finland in 2007 was 396 785 (The Social Insurance Institution of Finland, Population data, personal communication). Previous studies have found the prevalence of migraine in this age group to be 10% [10, 11], corresponding roughly to 40 000 individuals. Based on these figures and our data (see Figure 1), we can estimate that approximately 6% of children aged 12–17 years suffering from migraine were prescribed triptans in 2007.

Table 1

Entry of the triptans to the market in Finland. Month of receiving marketing authorization and admission of reimbursement of each drug according to first preparation on the market (Pharmaceuticals Pricing Board, Reimbursable triptans, personal communication) [15]

Drug and ATC-classification	Trade name and license-holder	Date of first marketing authorization	Approval of reimbursement	Formulations available January 2008	Authorization for use in children, status January 2008
Sumatriptan (N02CC01)	Imigran®, Glaxo Wellcome (injection)	June 1992 injection	June 1992 injection	Liquid for injection, tablet, nasal spray, suppository and dispersible tablet	Nasal spray 10 mg/dose: Extension of authorization to cover adolescents 12–17 years in August 2003.
	Sumatriptan ratiopharm® (tablet)	January 1993 tablet	January 1993 tablet		
	Imigran®, Glaxo Wellcome (nasal spray)	November 1996 nasal spray 10 mg/dose	October 2003 nasal spray 10 mg/dose		
Naratriptan (N02CC02)	Naramig®, Glaxo Wellcome	August 1997	January 1998	Tablet	Not authorized in children
Zolmitriptan (N02CC03)	Zomig®, AstraZeneca	July 1997	January 1998	Tablet, nasal spray, dispersible tablet	Not authorized in children
Rizatriptan (N02CC04)	Maxalt®, Merck Sharp & Dohme	August 1998	January 1999	Tablet, dispersible tablet	Not authorized in children
Almotriptan (N02CC05)	Almogran®, Almirall Prodesfarma	August 2000	December 2000	Tablet	Not authorized in children
Eletriptan (N02CC06)	Relert®, Pfizer	July 2001	November 2001	Tablet	Not authorized in children
Frovatriptan (N02CC07)	Migard®, Menarini International Operations	June 2002	October 2004	Tablet	Not authorized in children

Figure 1

Triptan use in children aged 6–17 years in 1994–2007. Figures include off-label use of sumatriptan and of the other triptans (zolmitriptan, rizatriptan, naratriptan, almotriptan, eletriptan and frovatriptan) and on-label use of sumatriptan in 2003–07. *Approval of nasal sumatriptan for adolescents 12–17 years old in August 2003. On-label use of sumatriptan (□); Off-label use of other triptans (▒); Off-label use of sumatriptan (■)

Figure 2

Sumatriptan off-label use in children aged 6–11 years and adolescents aged 12–17 years in 1994–2007 and on-label use of sumatriptan nasal spray 10 mg/dose in adolescents aged 12–17 years in 2003–2007. *Approval of nasal sumatriptan for adolescents 12–17 years old in August 2003. Off-label use age 6–11 years (■); Off-label use age 12–17 years (▒); On-label use 12–17 years (□)

Off-label use of the triptans

In all, 16 266 individual children and adolescents aged 6–17 years received reimbursement for off-label triptan use during years 1994–2007. Of these, 1881 (11.6%) were <12 years old. From 1994, the yearly number of paediatric triptan off-label users increased 10-fold during the study period, ending up at 1998 individuals in 2007. Growth of off-label use was relatively constant, but started to level-off in 2005–07. After the paediatric approval of sumatriptan nasal spray 10 mg/dose in 2003 the use of triptans other than sumatriptan, rizatriptan and almotriptan decreased, that of zolmitriptan almost by one third (data not shown).

The sumatriptan off-label use began in adolescents (12–17 years) and was extended to younger children (6–11 years) with a delay (Figure 2). In the younger age group

87.5% of the 1881 children prescribed a triptan were reimbursed for sumatriptan. Other triptans were rarely used in this age group.

Use after the approval of sumatriptan nasal spray

Sumatriptan nasal spray 10 mg/dose was approved for use in the age group of 12–17 years at the end of 2003. In the last 2 months of 2003, after the new paediatric formulation of sumatriptan had received reimbursement status (November 2003), 30 children were reimbursed for on-label use. During the next 4 years the on-label use of sumatriptan was extended, being 728 adolescents in 2007. However, during the same period sumatriptan off-label use

also increased almost by one third from 855 to 1119. The near doubling of the total number of children getting reimbursement for sumatriptan in 2004–07 was a result of increased off-label and on-label use.

After the paediatric formulation of sumatriptan became available, the number of children (6–11 years) receiving reimbursement for sumatriptan off-label use increased immediately two-fold from 2003 to 2004 (Figure 2). In 2007, 243 children aged 6–11 years old were prescribed sumatriptan off-label, the majority of them ($n = 187$; 77%) nasal sumatriptan in the paediatric 10 mg/dose nasal formulation. The number of children using the adult sumatriptan nasal spray (20 mg/dose) decreased from 105 in 2003 to 31 in 2007.

In 2007, the proportion of on-label use was 27.8% of the total triptan and 39.4% of the sumatriptan use in children 6–17 years, and 31% and 45.4% in the age group of 12–17 years, respectively. Despite the labelling of nasal sumatriptan for adolescents, almost three-quarters of triptan use was still off-label in the years 2005–2007. Both on-label and off-label use (use of other formulations than the labelled nasal spray) of sumatriptan in adolescents increased by 24% between the years 2005–07.

Discussion

The introduction of the first triptan labelled for children took place 11 years after its introduction for adults. Today, it still is labelled only to an adolescent subgroup of the paediatric population, only at a single paediatric strength and as one formulation. This has been the case although triptans represented a therapeutic benefit over existing treatments and migraine is not uncommon in the paediatric population. No official recommendations on triptan use in children were given during the study period, but several papers reviewing the treatment options and medical trials were published [18–25].

As a consequence of delayed paediatric authorization, off-label use became common and it continued to be so, or even increased, 4 years after the official labelling for adolescents. First marketing authorization of sumatriptan for adolescents seemed in this case to give a 'class certificate' of efficacy and safety of the triptans in children. This, together with the availability of a lower strength, led within 1 year to a doubling of sumatriptan off-label use in younger children under 12 years old. After the first year of the extension of the marketing authorization, on-label use grew in proportion to the total triptan use, and represented in this case only one fourth of the total use of triptans in children. The market size increase after labelling extension was modest.

Clearly, when the extension of authorization to children was delayed, physicians became accustomed to prescribing triptans off-label. Clinical experience from off-label use showed that triptans provided migraine relief in children

and no reports of major adverse effects appeared. The efficacy was also confirmed and safety suggested in several academic clinical trials during the years before and after paediatric labelling [26–30]. The prescribing physicians may not have felt a need to change the medication of their patients, when a labelled product appeared. It is also likely that the availability of only one paediatric formulation, a nasal formulation, has not helped conversion from mostly oral off-label use.

No studies documenting exactly the place of triptans in the treatment of migraine in the paediatric population have been published. It is generally accepted that NSAIDs, like ibuprofen, and acetaminophen (paracetamol), with demonstrated efficacy [31], represent the first line of treatment of paediatric migraine. It has been estimated that 30% to 60% of paediatric migraine patients need alternative treatments to the NSAIDs [32]. Presumably, a significant number of children and adolescents over the estimated 6% of the adolescent migraine population currently using triptans could benefit from them. Thus, there is still space for extending the paediatric use of triptans as the triptans most often prescribed to children after sumatriptan, zolmitriptan and rizatriptan, have not been labelled for children 13 and 12 years respectively, after their launch for adults. Likewise there is a need for labelling of oral and other age appropriate formulations also in strengths suitable for children below 12 years of age and the need for data on pharmacokinetics, efficacy and safety of the triptans in children from 6 years up was recognized in 2006 by the Paediatric Working Party (PEG) at the European Medicines Agency (EMA) [33].

The European paediatric regulation entered into force on 26 January 2007 [34], and paediatric development is required for any new drugs seeking marketing authorization within the EU, unless waived. Paediatric development is also a requirement when applying for line-extensions for existing patent-protected medicines. However, for medicines already well established on the market, with no need for a line extension, paediatric development becomes a voluntary measure, which is also the case for off-patent medicines. The modest increase in market size after paediatric labelling may not be interesting enough for the pharmaceutical industry to conduct paediatric trials when the paediatric off-label use is already wide, and off-label sales continue without further investment.

What this study seems to indicate, is that introducing a single labelled paediatric formulation of the oldest triptan to a part of the paediatric market 11 years after its authorization to adults does not lead to strong market penetration, even when it has remained the only triptan labelled for the paediatric population.

Reliability of the study

The coverage of the National Prescription Register from where the data for this study were derived is extensive.

Only medications funded directly by occupational health-care schemes of some employers (not very relevant for the paediatric population) and part of the purchases reimbursed by the local offices of the Social Insurance Institution, instead of the direct reimbursement in a pharmacy, are not recorded in the register. The register has remained similar since 1994. Changes in the reimbursement system do not influence the results of this study since the triptans have been reimbursable throughout the whole study period.

We had no data on the use of triptans before 1994, though the number of paediatric users right after the launch of sumatriptan in 1992 was presumably small as injection was the first formulation on the market (Table 1). The register does not contain information on the indication for the prescription, but migraine is the only indication for triptan use. Similarly, the lack of data on triptan use in health care institutions does not affect the results as triptans are mainly used in outpatient care (98% of bulk selling in 2007) [35].

Accuracy of the definition of triptan use in this study could be arguable. Triptan use each year was defined according to the number of individuals getting reimbursement for a triptan. One person could have several triptan purchases during one year and an adolescent 12–17 years old been prescribed triptan both off-label and on-label (nasal spray labelled 2003–07) during 1 year and would be included in both categories. However, such an effect seems minimal as the yearly changes in prescriptions seem consistent. Instead of measuring the number of persons receiving reimbursement for prescribed triptans, another option would have been to analyze the triptan use by the DDD/ATC methodology. The DDD (Defined Daily Dose) is the assumed average daily maintenance dose when drug is used by an adult and it is therefore inappropriate for a paediatric study [14].

In conclusion, when a new significant medicine becomes available in adults, off-label use in children seems to start slowly, increase more rapidly after more experience is available and, if labelling is delayed, to reach market size which is relatively little influenced by late appearance of a labelled product. Late labelling of old products has a limited effect on off-label use, and the market continues to be dominated by off-label sales. In the case of triptans, off-label use still overwhelmingly dominates, 16 years after the first one became available for adults and 5 years after it became available for a subgroup of children.

Competing Interests

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