Changes in availability of paediatric medicines in Australia between 1998 and 2002

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Aims

To determine changes in the availability of medicines for children in Australia and to determine the status of newly introduced chemical entities by age category.

Methods

Using the Australian Prescription Products Guide and the Schedule of Pharmaceutical Benefits, licensed medicines available in Australia in the calendar years 1998 and 2002 were examined.

Results

The total number of medicines licensed in Australia increased from 1544 to 1903, the number of licensed paediatric items increased from 579 (37.5%) to 725 (38.1%), and those both licensed for paediatric use and subsidized increased from 356 (23.1%) to 441 (23.2%). The number of medicines with formulations suitable for paediatric use increased from 861 (55.7%) to 967 (50.8%), and of these 382 (24.7%) and 466 (24.5%) were licensed for paediatric use. Of the 90 new orally available chemical entities licensed for adults only 12 (13%) were licensed for children. Three (3%) were licensed for the 0–28 days and 28 days to 23 months age groups, eight (9%) for 2–11 years and 12 (13%) for 12–18 years. An additional 14 orally available chemical entities previously only licensed for adults, were licensed for children by 2002.

Conclusions

There have been some improvements in medicines licensing for older children, but not for children under the age of two years.

Introduction

There has been extensive interest internationally in the availability of medicines for children. Most of this interest has focused upon use of medicines in an off-label manner (the use of medicines that have a Marketing Authorization (license) for indications not included in the Marketing Authorization) or unlicensed manner (the use of medicines which do not have a Marketing Authorization) [1–12]. The rate of off-label use of medicines in children varies from 10 to 29% in a primary care setting [1, 2, 6, 9, 11] to 20–39% in paediatric wards [4,

10] and 47–55% in neonatal intensive care [3, 7]. The rate of unlicensed medicine use in a primary care setting varies from 0.3 to 4% in primary care [1, 2, 6, 9, 11], to 7% in paediatric wards [4, 10] and 9.9–11% in neonatal intensive care [3, 7]. The extent of off-label and unlicensed drug use in children indicates restriction of the availability of medicines for children, with younger children affected to a greater degree.

A broader approach also examines the availability of medicines with formulations suitable for children and medicines subsidized for children, in addition to licens-

ing and labelling, on the basis that the cost of medicines and the ability to take them also determine accessibility [13, 14]. In Australia the licensing and labelling of medicines is regulated by the Therapeutic Goods Administration (TGA) [15], while the subsidizing of medicines is determined by the Pharmaceutical Benefits Scheme (PBS) [16]. The guidelines followed by the TGA are similar to those of the European regulatory agencies and the United States Food and Drug Administration (FDA), and also encompass many of the International Committee on Harmonization guidelines. Although all the formulations of a proprietary medicine are covered by the same license (marketing authorization) in Australia, each formulation undergoes an individual evaluation. This evaluation examines primarily issues such as bio-availability but might also include some evaluation of safety. Although many PBS listed drugs are unrestricted, where restrictions exist the indications must also be indications for which the drug is licensed. However, it is sometimes the case that a drug has a narrower PBS restriction than its' TGA-registered indication, because it has only been shown to be cost-effective in that narrower population. An unlicensed drug cannot be listed in the PBS Schedule.

Although it is known that in Australia 72% of medicines in 1994 and 1999 were unlicensed for use in children [14], the licensing status of newly introduced medicines is unknown. In Europe, only 10 of 45 new substances licensed between January 1995 and April 1998 were licensed for paediatric use [17]. In New Zealand between 1998 and 2002 there was an increase in the percentage of medicines licensed for paediatric use from 30.6% to 34.9%, but of the 100 new medicines with paediatric indications, only 36% were licensed for the 0–23 month age group and 69% were licensed for the 2–6 years age group [13]. This would suggest that older children may be obtaining greater access, but that little has changed for the younger age groups.

The aim of the present study was to determine changes in the availability of medicines for children in Australia by firstly: determining the licensing, suitability and subsidization status of all medicines marketed in Australia in 1998 and 2002; and secondly to determine the status of newly introduced chemical entities by age category.

Methods

Using the Australian Prescription Products Guide, licensed medicines available in Australia in the calendar years 1998 and 2002 were examined [18, 19]. Products such as condoms and diagnostic strips were excluded from the analysis. The following data on each product

licensed in 1998 and 2002 were identified: brand names, generic names, indications, types of formulation, paediatric licensing information and whether there was a dosage recommendation for children. The subsidy status of those medicines with paediatric licensing was identified from the February editions of the Schedule of Pharmaceutical Benefits 1998 and 2002 [20, 21]. If a paediatric formulation was subsidized in that particular year, the conditions and restrictions on prescribing the subsidized products were recorded. The medicines were then further categorized as: medicines with suitable formulations, including injectable, dermal, ear/eye, liquid, soluble and powdered oral preparations; suitable medicines licensed for paediatric use; and suitable medicines that were both licensed for paediatric use and also subsidized. All of the licensed items were then classified according to their route of administration as: suitable oral, i.e. oral formulations able to be taken by an infant or young child, including liquid, powder, oral spray and soluble tablets; unsuitable oral, included tablets, capsules and other solid formulations; ear/eye, i.e. topical otic or ocular medications; inhaler, i.e. aerosolized medicines for inhalation; injectable; nasal, i.e. topical or aerosolized nasal medication; rectal; dermal, i.e. medicines applied topically to the skin; and other preparations.

Products withdrawn or introduced into the licensing system for paediatric administration were identified and classified according to their formulation types and therapeutic indications. The changes in total number of each formulation and product (withdrawn or introduced) between the years 1998 and 2002 were determined for each therapeutic indication by comparing the data from the year 1998 with that from 2002. A search for therapeutic equivalents (generics) and therapeutic alternatives (medicines indicated for the same purpose) was made using the spreadsheet and Australian Prescription Products Guide. Only medicines licensed for paediatric use were considered acceptable alternatives. For newly introduced medicines, their dosing information was further analysed by classifying the number of items licensed for the age groups: 0–27 days, 28 days to 23 months, 2–11 years and 12–18 years [22].

Medicines that were subsidized for paediatric use in the calendar years 1998 and 2002 were compared. Those medicines that were withdrawn from the subsidy system in the interim period were identified. A search was made from the 2002 database for suitable licensed and subsidized paediatric therapeutic equivalents and alternatives.

In order to determine the status of each chemical entity, all the oral formulations licensed in Australia were identified from the information on the Microsoft

Excel Spreadsheet and were listed in alphabetical order of their chemical entities. The availability of suitable oral formulations, the paediatric licensing status and the subsidized conditions and restrictions of each chemical entity were determined.

Results

Between 1998 and 2002, there was an increase in the total number of medicines licensed in Australia from

Figure 1

The total number of medicines licensed in Australia between 1998 and 2002. Total medicines licensed in Australia (▨), medicines with formulations suitable for children (▩), medicines with suitable formulations licensed for children (■), medicines subsidised, licensed and suitable for children (▤)

1544 to 1903 (Figure 1). The number of medicines with paediatric licensing increased from 579 (37.5%) to 725 (38.1%), and those both licensed for paediatric use and subsidized followed a similar trend and increased from 356 (23.1%) to 441 (23.2%). The number of medicines with formulations suitable for paediatric use increased from 861 (55.7%) to 967 (50.8%), and of these 382 (24.7%) and 466 (24.5%) were licensed for paediatric use. The number of medicines with suitable formulations both licensed and subsidized for paediatric use increased from 185 (12.0%) to 226 (11.9%).

The number and percentage of paediatric licensed suitable oral formulations, inhaled formulations and dermal formulations increased from 1998 to 2002 (Table 1). In addition, the number of paediatric licensed suitable oral formulations and inhaled formulations subsidized for paediatric use increased. There was a small decrease in the number of ears/eyes formulations licensed for paediatric use, and a small increase in the number subsidized. There was an increase in the number of unsuitable oral formulations with paediatric licensing and subsidy. For injectable formulations there were 43 more items licensed for paediatric use, with seven of these licensed and subsidized. There was minimal change in the number of rectal formulations available that were licensed or subsidized for paediatric use.

Over the 5 year period between 1998 and 2002, there were substantially more paediatric-licensed medicines introduced than withdrawn. One hundred paediatric medicines were withdrawn compared with 249 introduced. Several types of agents had considerably more numbers introduced than withdrawn. These included

Table 1

Types of formulations that were licensed and/or subsidized for paediatric use

	Total	1998		Total	2002	
		Licensed for paediatric uses, n (%)	Licensed and subsidized for paediatric use, n (%)		Licensed for paediatric uses, n (%)	Licensed and subsidized for paediatric use, n (%)
Unsuitable oral	682	197 (28.9%)	171 (25.1%)	936	259 (27.7%)	215 (23.0%)
Suitable oral	102	74 (72.5%)	57 (55.9%)	131	99 (75.6%)	80 (61.1%)
Ears/eyes	93	10 (10.7%)	3 (3.2%)	90	8 (8.9%)	4 (4.4%)
Inhalers	48	38 (79.2%)	28 (58.3%)	64	53 (82.8%)	39 (60.9%)
Injectable	470	236 (50.2%)	82 (17.4%)	541	279 (51.6%)	89 (16.4%)
Nasal	9	7 (77.8%)	6 (66.7%)	14	8 (57.1%)	5 (35.7%)
Rectal	15	3 (20.0%)	2 (13.3%)	17	2 (11.8%)	2 (11.8%)
Dermal	106	14 (13.2%)	7 (6.6%)	99	17 (17.2%)	7 (7.1%)
Vaginal	15	0 (0%)	0 (0%)	9	0 (0%)	0 (0%)
Other unsuitable	1	0 (0%)	0 (0%)	0	0 (0%)	0 (0%)
Other suitable	3	0 (0%)	0 (0%)	2	0 (0%)	0 (0%)

anaesthetic, antibacterial, anticonvulsant, antiviral, H₂ histamine receptor antagonists and vaccines (Table 2). However, fewer antihistamines, antineoplastic and systemic corticosteroid preparations were introduced than withdrawn. For 50 of the 100 paediatric-licensed formulations withdrawn between 1998 and 2002, identical formulations were available. For the remainder, different generic equivalent medicines were identified for 18 items, but seven were for a different route of administration. Amongst the 32 items withdrawn with no generic equivalent medicines, 29 had therapeutic alternatives. There were no medicinal therapeutic alternatives available for gonadorelin, tolazoline hydrochloride and diethylpropion hydrochloride.

The 249 licensed paediatric medicines introduced between 1998 and 2002 comprised 75 chemical entities (Table 3). Of the 75, 31 were licensed for 0–27 days of age, 35 for 28 days to 23 months, 59 for 2–11 years, 73 for 12–18 years. The largest therapeutic group was infectious diseases with 18 agents, with eight of these agents being for the treatment of HIV infection. Other predominant groups were vaccines, nervous system and anaesthetic agents.

When medicines that were subsidized for paediatric use in 1998 and 2002 were compared, 72 items had been withdrawn from the subsidy status. Forty-eight of the 72 items were removed because they were no longer licensed for paediatric use in Australia. Forty-two out of the 72 withdrawn items had identical formulations that were subsidized for paediatric use, 11 had different

Table 2

Types of paediatric licensed medicines that were withdrawn and introduced according to therapeutic indication in Australia between 1998 and 2002

	Withdrawn	Introduced
Anaesthetics	4	13
Analgesic	6	6
Antibacterial	29	67
Anticonvulsants	6	15
Antidepressants	2	2
Antifungal	2	4
Antihistamines	5	0
Antihypertensives	1	1
Antineoplastics	3	2
Antiviral	1	19
Bronchodilator	9	12
Calcium channel antagonist	0	2
Corticosteroid inhalation	2	4
Corticosteroid nasal preparation	1	3
Corticosteroid systemic preparation	3	1
Corticosteroid topical preparation	0	3
Diuretic	3	5
H ₂ -receptor antagonist	0	12
Hypoglycaemics	0	2
Proton pump inhibitor	0	2
Vaccine	7	23
Vasodilator	2	0
Other anti-asthma agents	0	2
Other	14	49
Total	100	249

Table 3

Chemical entities acquiring paediatric licensing between 1998 and 2002

	Percentage of chemical entities newly licensed for each age group					% total
	0–27 days	28 days–23 months	2–11 years	12–18 years	n	
Anti-infectives	39	39	67	100	18	24
Vaccines	0	20	70	80	10	13
Nervous system	22	22	67	100	9	12
Anaesthetic	50	63	100	100	8	11
Respiratory and allergy	43	43	71	100	7	9
Contrast media	50	50	100	100	4	5
Alimentary tract and metabolism	67	67	100	100	3	4
Hyperlipidaemia/blood disorders	100	100	100	100	3	4
Antivenom	100	100	100	100	3	4
Oncology and immunology	67	67	100	100	3	4
Dermatology	0	0	50	100	2	3
Musculoskeletal	50	50	50	100	2	3
Antidote	50	100	100	100	2	3
Endocrine/hormone	100	100	100	100	1	1
All categories	41	47	79	97	75	100

Table 4

Availability of suitable oral formulations according to chemical entities

	1998	2002
Orally available chemical entities	423	467
Chemical entities with suitable paediatric formulations	77 (18%)	85 (18%)
Chemical entities with paediatric license	133 (31%)	148 (32%)
Paediatric licensed chemical entities with suitable formulations	55 (13%)	59 (13%)
Chemical entities that were suitable, licensed and subsidized for paediatric use	40 (9%)	44 (9%)

generic equivalent medicines (three of these were for a different route of administration) and therapeutic alternatives were available for the remaining 19 items that were no longer subsidized for paediatric use.

There was a net gain of 44 orally available chemical entities from 423 in 1998 to 467 in 2002. The numbers that were suitable, licensed or subsidized for paediatric use all increased (Table 4). No obvious changes were observed in the percentages in the five years. Ninety orally available new chemical entities were introduced over the 5 year period. Twelve (13%) had paediatric licensing. Of the 90 new orally available chemical entities, three (3%) were licensed for 0–27 days age, three (3%) for 28 days to 23 months, eight (9%) for 2–11 years and 12 (13%) for 12–18 years. In addition a further 14 oral chemical entities licensed only for adults in 1998, were licensed for children by 2002, with only six (43%) licensed for children under 2 years of age.

Discussion

Despite changes to the regulatory procedures for the registration of medicines for children in the United States, there has been little evidence in the present study of any flow-on benefits to children in the younger age groups. Between 1998 and 2002 there was a decrease in the proportion of medicines with suitable formulations, and no significant improvement in proportions of medicines licensed and subsidized for children, although there was an improvement in the total number of medicines available. Of the paediatric-licensed medicines withdrawn, three had no alternatives available for children. Of the chemical entities that acquired paediatric licensing, the majority were indicated for older children, with only 47% having dosing information for children less than 2 years of age. For the new oral chemical entities introduced, a minority had paediatric licensing and few were licensed for use in the younger age groups. Although not all chemical entities would be of use in

the treatment of childhood disease, the proportion that is available appears to be excessively low.

In Australia, it has been previously reported that there is inadequate dosing information for children and that many pharmaceuticals that provide dosing information are not available in a suitable formulation [14]. Recommendations have been made to improve the licensing of medicines for children [23]. However, an assessment of the licensing and suitability of newly introduced medicines has not been reported previously. The results of the present paper indicate that little has changed in relation to the proportion of medicines available for children in Australia between 1998 and 2002. In order to achieve an improvement in the availability of medicines for children, inducements and legislation similar to those operating in the United States may be required.

The Food and Drug Administration in the USA provided financial incentives for the development and marketing of medicines for children. In the Food and Drug Administration Modernization Act 1997, the FDA waives fees for supplemental application for paediatric approval for new drugs that are already approved for adult use [24, 25]. Furthermore, 6 additional months of exclusivity or patent protection is given to manufacturers conducting paediatric studies on drugs. In 1998, the FDA published a priority list of drugs where further paediatric studies would be beneficial. These efforts should encourage the pharmaceutical industry to study the use of medicines in children, but it may transpire that the only effect of the legislation is to improve the availability of medicines to the older age groups of children, similar to the findings of the present study.

Proposed changes in licensing requirements by the European Medicines Evaluation Agency would press the manufacturers to provide detailed data for prescribing for children wherever the drug is likely to be used for them [26]. The manufacturers would also be urged to develop formulations that are suitable for children. In

addition, a European Network for Drug Investigation in Children has been established to facilitate the development of pharmaceutical research in children [27]. This approach differs to that of the United States, but as these measures have not been implemented, their impact cannot be evaluated.

In 1997 the Australian Drug Evaluation Committee, an advisory committee of the TGA, published a report into the licensing of medicines for children in Australia [28]. Some of the recommendations included: implementing guidelines for the registration of drugs in children, encouraging the inclusion of children in clinical trials and requesting the updating of product information to include information on paediatric use. In addition, the TGA is prepared to waive evaluation fees for orphan drugs (a drug for which the patient population has a prevalence of less than 2000). For some medicines, an application to extend the indication of an approved product to include the treatment of children would fulfil this criterion. However, these initiatives did not include the use of incentives, unlike the approach in the United States, nor is there any obligation for a manufacturer to provide paediatric data.

Over the same time period in New Zealand the number of orally available chemical entities licensed for children declined by six, compared with an increase of 15 in Australia [13]. In New Zealand the overall percentage of orally available chemical entities licensed for children remained at 37.4% compared with a slight increase from 31% to 32% in Australia. Despite the degree of economic integration and sharing of regulatory information between the two countries there are some notable differences in the availability of medicines. In New Zealand there are more chemical entities available, while in Australia there are more medicines, reflecting a greater number of generic medicines.

A practical problem for the pharmaceutical industry is that to administer a drug orally to infants and children under the age of 2 years a liquid formulation is desirable [25, 29]. A liquid dosage form is needed to accurately measure doses according to body weight. Chewable tablets are an acceptable alternative in children 2 years and older [30]. Single unit tablets or capsules are commonly split to facilitate paediatric use. However, the effect of splitting tablets or capsules on the drug effects and toxicity must be carefully assessed. The introduction of fast dispersing tablets and other novel formulations should be encouraged since these facilitate the administration of lower doses to children. Although the development of these delivery systems is expensive, there could be a financial incentive because the elderly and disabled populations could also benefit from these. Similarly,

injections with strength and quantities appropriate for children should be introduced to minimize the risk of medication administration errors.

The purpose of the licensing systems is to ensure safety, efficacy and quality in medicines used in children. Controlled clinical trials are necessary to minimize the potential risks that children are exposed to in the administration of drugs and determine the most appropriate dosage for children. Although it is more difficult to organize clinical trials in children than in adults, adequate trials can be carried out in the paediatric age groups [27]. Furthermore, suitable paediatric formulations must be developed in order to accurately administer medicines to children. If the widespread use of unlicensed or off-label medicines persists, children will continue to be denied the same right as adults to receive drugs that have been fully tested for their safety, efficacy and quality.

In conclusion, there has been no change in the proportion of medicines licensed for children in Australia and a decrease in the proportion of medicines with a formulation suitable for young children. The majority of newly introduced medicines were for the treatment of infections and dosing information was predominantly for children over the age of 2 years.

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