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Original Article

A Survey of Off-label and Unlicensed Prescribing Drugs at a Community Hospital in Thailand

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Abstract The purpose of this study was to determine the extent of off-label and unlicensed prescribing drugs by using all computer-based prescription records of adults who visited the outpatient department in a community hospital over the 2-week period. Information on licensed product was derived from package insert which was approved by Food and Drug Administration (FDA), Thailand, and was used to determine whether prescribed drugs were licensed, unlicensed, or in an off-label manner. A total of 3,155 items were prescribed and there were 113 different drugs. There were no prescribed unlicensed drugs. Of prescribed items, 85% were licensed drugs and prescribed on-label while 15% were prescribed off-label. The most common off-label prescribing was associated with dosage/frequency (438 items; 14%) and 1% was associated with indication. The most common off-label prescribed items were used for respiratory disorders, followed by those for cardiovascular disorders.

Keywords: community hospital, drug use, off-label drug, unlicensed drug

INTRODUCTION

Before a drug is launched in the market, the favorable balance between benefit and harmful effects has to be demonstrated. The purpose of licensing is to ensure that medicines are marketed only after safety, efficacy, and quality approval. When a drug is prescribed outside these parameters, this support is lacking and the off-label or unlicensed prescribing may be occurred.

Off-label prescribing refers to prescribing a registered medicine for a use that is not included or is disclaimed in the product information, or uses outside the terms of its licensed product, with differences in dose (greater dose), frequency (more often), clinical indications (not described in the licensed), age groups (outside the age range for which the product is licensed), administration by alternative route, formulation not being approved for use, or use with contra-indication.[1-5] Unlicensed drug use is the use without a product licensing, modification of licensed drugs (such as crushing tablets to prepare a suspension), drugs that are licensed but the formulation is manufactured under a special licensing (such as a smaller dose for children being formulated from an adult preparation), new drugs available under a special manufacturing licensing (such as caffeine injections for apnea of prematurity), use of chemicals as drugs when no pharmaceutical preparation is available, drug uses before a licensing has been granted, or imported drugs (drugs imported from a country where they are licensed).[1-5]

There has been published about the extent of, and problems associated with, the off-label

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and unlicensed use of medicines, particularly in children.[2,4] On general pediatric surgical and medical wards, 36% of children were received at least one drug that was either unlicensed or off-label during admission in the hospital.[3] A study of children's wards in five European countries found that almost half (46%) of all prescriptions were either unlicensed or off-label prescriptions.[1] In non-hospital settings; such as office based pediatric practice, either unlicensed or off-label uses were found. Among French office based pediatricians,[4] 56% of children received at least one drug that was either unlicensed or off-label also in general practice in the English Midlands,[5] of the 3,347 prescriptions items, 0.3% were unlicensed medicines and 10.5% were licensed medicines prescribed in the off-label way. Also, there have been many reports about off-label prescribing in some groups of adults such as the pregnant[6] or the off-label use in the group of drugs such as selective serotonin reuptake inhibitors (SSRIs).[7] In Thailand, there are no reports about off-label and unlicensed prescribing drugs, therefore the prevalence of this topic may need to be further surveyed.

METHODOLOGY

Study Design

A retrospective analysis was performed with all computer-based prescription records of adult who visited the outpatient department over the 2-week period from 1st September to 14th September, 2006 at a 10 beds community hospital.

Prescription Selection

The computer-based prescription records which were recorded the diagnosis and also prescribed drug(s) of adult outpatients were recruited in the study. Information from the computerized records of prescriptions were included patient's reference, patient's age, sex, issued date of the prescription, drug, formulation, indication, dose, quantity, and route of administration. Other devices provided to their treatment; for example, disposable needle, disposable syringe, or gauze pad, were excluded.

Patient Selection

Outpatients, who visited to the hospital between 1st and 14th September, 2006 and were more than 12 years of age, were selected.

Reference Source for Licensing

Information on the product license was derived from the package insert of each product which was already approved by the Food and Drug Administration (FDA), Thailand. This information was then used to determine whether prescribed drugs were licensed, unlicensed (without a product license), or used in an off-label manner (outside the terms of their product license). Each prescription was compared to the data available in the package insert and each off-label prescription was categorized into 4 groups as previously described in other studies as age, indication, dose, or route of administration. Unlicensed uses were also described; for example, modification of licensed drugs, drugs that were licensed but the formulation was manufactured under a special license.

RESULTS AND DISCUSSION

Over the 2 weeks study period, there were 1,328 outpatients who visited the hospital for totally 1,603 times. When patients aged more than 12 years with available diagnosed prescription records were considered, there were then 682 adult patients with 745 visiting times were recruited. These remaining patients received 3,155 prescribed items, involving 113 different drug lists. Each patient received between 1-15 different drug lists and the ages of the patients ranged from 13 to 88 years old. Of the 3,155 prescribed items, 2,679 (85%) were licensed medicines being prescribed on-label and 476 (15%) were licensed medicines being prescribed off-label (Table 1). There were no unlicensed (without a product license) drugs being prescribed. According to the off-label prescribing, there were 18 off-label prescribed drugs. The most frequently drugs prescribed in an off-label manner are shown in the Table 2. Off-label prescribed medicines can be categorized into 4 groups according to

age of patients, indication, dose, or route of administration. In this study, the most frequent categories of off-label prescribed medicines were respected to dose/frequency (438 items; 14%) and clinical indication (38 items; 1%). Examples of off-label prescribed items are summarized in the Table 3.

There were 18 different drugs involving in off-label prescribing. Many drugs were prescribed according to the terms of the license but in off-label way. For example, atenolol 100 mg, was prescribed for 42 patients and the recommended dose from the package insert was 50-100 mg/day. Thirty six patients were prescribed 100 mg/day according to the terms of the product license, but 6 patients were prescribed to take 150-200 mg/day and this was considered as an off-label prescribing. Summary of off-label prescribed items by drug classification is presented in Table 4.

Another example of off-label with respect to dose was bromhexine for cough and cold remedies. It was usually prescribed 1 tablet 3 times a day in the practice but it was stated in the package insert as 1 tablet, 4 times a day.

Table 1. Summary of licensed status of prescribed items

Licensed status	No. of prescribed items (%), (n = 3,155)
Licensed, on-label	2,679 (85)
Licensed, off-label	476 (15)
- dose	438 (14)
- indication	38 (1)
Unlicensed	0 (0)

Table 2. Summary of most frequently items prescribed in an off-label manner

Drug lists	No. of off-label prescribed items (%), (n = 476)
Bromhexine, 8 mg	94 (19.7)
Carminative mixture	78 (16.4)
Vitamin B complex	75 (15.8)
Brown mixture	56 (11.8)
Gemfibrozil, 600 mg	28 (5.9)
Hydroxyzine, 10 mg	28 (5.9)
Norfloxacin, 400 mg	24 (5.0)
Nifedipine, 20 mg SR	20 (4.2)
Aspirin, 300 mg	16 (3.4)
Dextromethorphan, 15 mg	10 (2.0)
Squill ammonium carbonate	8 (1.7)
Atenolol, 100 mg	6 (1.3)

Table 3. Examples of off-label prescribed items

Drug lists	Dosage/indication from prescription record	Recommended dose/indication from the package insert
Atenolol 100 mg	1 tablet, 2 times daily or 1 ½ tablets once daily	½ - 1 tablet/day (50-100 mg/day)
Bromhexine 8 mg	1 tablet, 3 times a day	1 tablet, 4 times a day
Ketoconazole 200 mg	1 tablet, 2 times a day	1 tablet once a day or 2 tablets daily as a single dose
Norfloxacin 400 mg	Acute cystitis: 1 tablet (400 mg), twice daily for 5 or 7 days	Acute cystitis: 200 mg twice daily for 3 days
	Gastrointestinal tract infection: 1 tablet (400 mg), twice daily for 3 days	Gastrointestinal tract infection: 1 tablet (400 mg), twice daily for 5 days
Aspirin 300 mg	Antiplatelet aggregation	Relief of pain and fever
Sodium bicarbonate	Use in renal failure for metabolic acidosis	Antacid, dyspepsia
Norfloxacin 400 mg	Hyperplasia, Calculas	Urinary tract infection, bacterial gastroenteritis, gonorrhea

Table 4. Summary of off-label prescribed items by drug classification

Drug classification	No. of off-label prescribed items (%), (n = 476)
Respiratory drugs: bromhexine, Brown mixture, dextromethorphan, squill ammonium carbonate	168 (35.3)
Cardiovascular drugs: gemfibrozil, nifedipine, aspirin 300 mg, atenolol, verapamil	71 (14.9)
Anti-infectives: norfloxacin, metronidazole, ketoconazole, trimethoprim 80 mg + sulfamethoxazole 400 mg	30 (6.3)
Others: carminative mixture, vitamin B complex, hydroxyzine, sodium bicarbonate, mefenamic acid	207 (43.5)

This can be presented as off-label item but whether it was inappropriate. It may be due to the different physicians, pattern of prescribing, the experience or the knowledge of the physician.

However, there were possible limitations in the study. Firstly, there was incomplete data from computer record prescribing system. Due to the retrospective survey, there were some missing data from the prescription records such as laboratory results and others. The second limitation was the information from package insert which was not clear such as dosage for each indication. Also, some information of the approval dose or indication did not correspond with the recent recommendation. It was therefore difficult to determine how the unlicensed or off-label way was using.

Although off-label therapy seems to be legal, physicians must be aware of potential medical and legal hazards of these uses. A summary of off-label uses shall be collected and considered in particular to promote appropriate uses. Also, collaboration between FDA and drug manufactures should be concerned to update the information in package insert.

REFERENCES

1. Conroy S, Choonara I, Impicciatore P, *et al.* Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ* 2000; 320: 79-82.
2. Gazarian M, Kelly M, McPhee JR, *et al.* Off-label use of medicines: consensus recommendations for evaluating appropriateness. *MJA* 2006; 185: 544-8.
3. Turner S, Longworth A, Nunn AJ, *et al*. Unlicensed and off label drug use in paediatric wards: prospective study. *BMJ* 1998; 316: 343-5.
4. Chalumeau M, Treluyer JM, Salanave B, *et al*. Off label and unlicensed drug use among French office based paediatricians. *Arch Dis Child* 2000; 83: 502-5.
5. McIntyre J, Conroy S, Avery A, *et al*. Unlicensed and off label prescribing of drugs in general practice. *Arch Dis Child* 2000; 83: 498-501.
6. Rayburn WF, Farmer KC. Off-label prescribing during pregnancy. *Obstet Gynecol Clin North Am* 1997; 24: 474-8.
7. Stone KJ, Viera AJ, Parman CL. Off-label applications for SSRIs. *Am Fam Physician* 2003; 68: 498-504.