Comparative Analysis of Patient Package Inserts of Local and Imported Anti-Infective Agents in Palestine

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Abstract

Background and Objective: The patient package insert is an important source of drug information. The aim of this study was to evaluate and compare the PPI of the anti-infective agents manufactured in Palestine with the imported equivalents. **Method:** The selection criteria generated 15 different anti-infective agents available as 36 locally manufactured products and 15 imported equivalents. The design of the patient package insert was evaluated in terms of the number of words used in eight main headings and the presence or absence of certain information regarding nine statements. **Results:** Inserts of locally manufactured products have significantly fewer words than those of imported products with respect to warnings, dosage and administration, and side effects. The most significant difference was found in the warnings. Moreover, differences were found between inserts of local and imported products in terms of the presence of the nine informative statements. Locally manufactured products did not mention inactive ingredients, clinical pharmacology or date of last revision, but all of them provided information on the use of the drug during pregnancy and lactation and on the duration of therapy. However, in general they provided less information than the imported equivalents. **Conclusion:** Palestinian authorities and local manufacturers should implement appropriate measures to regulate the quality and quantity of information in the patient package insert of locally produced anti-infective agents. PPI improvement will better direct health practices to the benefit of the patients.

Key words: patient package insert, evaluation, Palestine, drug information.

Introduction

The patient package insert (PPI) is important for providing essential drug information for patients taking over-the-counter as well as prescription-only medications. In developing countries, the PPI is considered an important source of drug information for health-care providers as well, because of a limited ability to access up-to-date information about drugs. In addition, studies have shown that the PPI helps bridge the information gap between health care providers and patients and enhances patients' knowledge about medications [1,2]. The quality and quantity of information available in the PPI has been shown to influence patients' compliance and satisfaction [3,4]. There are also indications that patients who read the PPI are more likely to follow the instructions, especially if the information in the PPI agrees with the instructions of the physician and/or pharmacist [5]. A study carried out in Denmark found that patients may be confused by inconsistent information in PPI, which leads to reduced compliance [6].

The design and the amount of information in the PPI are usually regulated by the legislative health authorities. The PPI should increase patient's awareness of medication-related issues, contribute to the safe and correct use of the medication, and help in the success of the treatment plan. The European Directive 2001/83/EC of November 2001 requires stipulates that in all European Union member states every drug should include an easily legible and clearly comprehensible package insert [7]. The European Commission provides guidelines for the contents of package inserts, including style and terminology [8,9]. In comparison to Europe, package inserts in the USA focus considerably more on medical specialists. American package inserts frequently feature smaller font and many technical terms and consist of up to six A4 pages [10,11]. Despite all efforts, PPI are still criticized in USA, many European countries [12], and Australia [13,14]. For example, it was reported that decreased compliance was found in patients who felt frightened after they had read the package insert [13]. Some experts have suggested that the PPI for drugs intended for children or pregnant women should include symbols and special features [15].

In Palestine, five local pharmaceutical companies produce about 1000 of the different medical products on the Palestinian market. Besides the locally manufactured medical products, many imported drugs are registered in the Palestinian market. The Palestinian Ministry of Health (MOH) recommends that all marketed medications be supplied with a PPI that is written in both Arabic and English, but there are no regulations regarding the quality or the quantity of the information, design and wording of the PPI.

In this study we aimed to evaluate and compare the PPI contents of a group of selected anti-infective medications manufactured locally to the imported equivalents in the Palestinian market.

Materials & Methods

Inclusion Criteria

Anti-infective agents were selected for study because they are commonly utilized and because infectious diseases are one of the most common causes of mortality in Palestine [16]. The inclusion criteria were as follows: (i) manufactured by at least two local pharmaceutical companies; (ii) have an imported equivalent; (iii) available in oral solid form; (iv) registered in the department of pharmacy at the Palestinian MOH; (v) available in the local market. Based on these criteria, 15 different anti-infective agents were included in this study: amoxicillin, amoxicillin/clavulanic acid, azithromycin, clarithromycin, metronidazole, terbinafin, ketoconazole, trimethoprim/sulfamethoxazole, cephalexin, cefuroxime, mebendazole, doxycycline, ofloxacin, ciprofloxacin and fluconazole. The imported products selected in this study were the most popular equivalents that are manufactured outside the Palestinian authority areas. The popularity of a certain imported product was judged through a phone survey of 100 randomly selected community pharmacies in Palestine. In this survey, the pharmacists were asked to state the most commonly dispensed imported equivalent(s) for each of the studied agents.

Evaluation and Assessment of the PPI

The PPIs were initially evaluated according to the general design and quantitatively evaluated by two methods. The first was a simple word count of eight major headings: description, indications, contraindications, warnings, drug interactions, side effects, dosage and administration, and storage. The "warning" heading included both the caution and precaution headings. The words under each of the eight tested headings were counted manually.

The second method of evaluation was carried out by using a scoring method for the presence of information on the following nine statements in the PPI: inactive ingredients, therapeutic class, clinical pharmacology, use during pregnancy and lactation, overdose, missed doses, duration of therapy, instructions not to consume after the expiration date, and the date of last revision. Presence of the information was scored as 1 and its absence as 0. The total score was calculated for each anti-infective agent. The percent score was calculated as a percentage of the possible maximal score for each local company as well as for the imported products.

All data were entered into the statistical package for social sciences (SPSS) version 13. Mean score and mean word count was calculated for locally produced and for imported anti-infective agents. Statistical comparison was carried out using Student's t-test.

Results

General evaluation of the PPI

The selected anti-infective agents were available in the Palestinian market as 36 local and 15 imported products (Table 1). The 36 local products are produced by four pharmaceutical companies designated as A (4 products), B (8 products), C (10 products), and D (14 products). The 15 most popular imported anti-infective agents belong mainly to American and European companies (Table 1).

All the inserts of all local and imported products were printed in both Arabic and English. In the local products, Arabic was on one side of the insert and English on the other. In contrast, most of the imported products had both languages on the same side. Inserts of locally manufactured products used smaller font than those of the corresponding imported products.

The design of the inserts was also evaluated. The criteria used to assess design included size of the leaflet, text font size, and size and colour of headings. The overall design was different from one local company to another and even between different medications produced by the same company. With the exception of one local company, the headings in all local inserts were printed in black. In addition, the inserts of the local products differ from those of the imported equivalents in the order and terminology used for some headings.

Word count

We compared the word counts of the eight headings in the PPI of local and imported products. Significant differences in word count were found between the local and the imported products in the headings "warnings", "side effects", and "dosage and administration" with P values of 0.008, 0.016, and 0.024, respectively (Table 2A,B). The word counts in table 2 were analyzed vertically and horizontally. The mean word counts for the "warnings" heading was 64.7 words in all local inserts combined and 167.7 words in all imported products combined, which is a 2.5-fold difference. Similar findings were observed in the "side effects" and "dosage and administration" headings (table 2).

We also counted all words in each insert. With the exception of azithromycin, the total number of words in the eight tested headings was greater in the imported than in the local products (P= 0.01). The imported amoxicillin/clavulanic acid, terbinafin, ofloxacin, and cephalexin inserts had three- to fourfold more words than their local equivalents (Table 2A,B). Amoxicillin/clavulanic acid had the highest word count compared to the other drugs, but the imported product had 2989 words whereas the local product had only 582 words.

Analysis of scores

All inserts were also evaluated using the scoring method. The total score was 65.4 for the locally manufactured anti-infective agents and 81 for the imported equivalents (P= 0.02) (Table 3). None of the inserts achieved a full score. None of the local products had information on "inactive ingredients," "clinical pharmacology" and "date of last revision," whereas one third to one half of the imported products provided this type of information (Table 4). By contrast, all inserts contained instructions about use during pregnancy and lactation, overdose and duration of therapy (Table 4). However, the information concerning pregnancy and lactation in the local products was given under different headings, such as "contraindications," "warnings" or "precautions," or otherwise stated separately as follows: "inform your physician if you are pregnant or breastfeeding." In addition, local products differed from imported products in the amount of information. Local products did not explain whether that can be used during pregnancy. In contrast, the imported products provide detailed information for both patients and health-care providers on the use of the medication during pregnancy and lactation. The pattern was similar for the statement pertaining to "overdose" and its consequences and first aid. "Go to the hospital in case of overdose", and/or "do not induce vomiting" are the most common instructions found in the inserts of most local anti-infective agents. In contrast, inserts of imported products mentioned in details the effects expected from overdose and the proper emergency treatment. Regarding the "duration of treatment", most inserts of local products state: "duration is as directed by the physician," or "do not stop the medication without informing the physician." By contrast, most imported products informed patients about how long the medication should be taken.

Inserts of imported cefuroxime, amoxicillin/clavulanic acid and metronidazole have the highest total score on the nine statements (Table 3). For the local products, amoxicillin/clavulanic acid has the highest score (5.5; Table 3). Among the four local pharmaceutical companies, the highest percent score (percent of the maximal score) was 51.4% and the lowest was 8.4%, compared to 60% for the imported pharmaceutical companies combined (Table 4).

Discussion

We found significant differences in the quantity and quality of information in the inserts of locally produced compared to imported anti-infective medications. Although the word counts for the "indications" were not significantly different, there were differences in the quality of the information. Most of the local anti-infective agents mentioned the "indications" in general terms: "for the treatment of infections". However, in the imported products, the "indications" heading included, in most of the cases, the sites and types of infections and in a few cases the name of susceptible micro-organisms. Differences between inserts of local and imported products were also found in statements regarding inactive ingredients, clinical pharmacology and date of last revision. It is important to list the inactive ingredients, such as sodium salts or artificial sweeteners, for the sake of patients with certain types of diseases or allergies. Not mentioning the date of last revision of the insert might negatively influence the patient's and physician's trust in the product. The differences between the local companies in the amount and type of information in the insert indicates that there is no governmental supervision over locally produced anti-infective agents, and probably other drugs as well, and that regulation is required to ensure that patients are provided sufficient information. Physicians and pharmacists who depend on locally written PPI as a source of drug information may not be able to provide good patient counselling and to obtain up-to-date information. For example, use of medications during pregnancy and lactation was not fully explained in inserts of local anti-infective products. Lack of detailed information about overdose makes health care providers and/or the general public unable to make the best decisions in case of poisoning. Early management of poisoning is important for good prognosis, and it cuts down on hospital visits and medical expenditure.

Inadequate information in the PPI has been reported by authors in different countries. In a study carried out in Saudi Arabia, the authors found that there was substantial disagreement in information between generic package inserts and the British National Formulary and the package inserts of the brand products marketed in Saudi Arabia [17]. In another study of non-steroidal anti-inflammatory agents marketed in Saudi Arabia, the authors showed that inserts of Saudi-marketed products generally conveyed limited and incomplete information compared to their counterparts marketed in USA [18]. In the USA, it was shown that PPI do not fully meet the federal regulations [19]. A European study found substantial disagreement in the materials available to prescribers and patients in different countries [20]. A study in Perugia found that all people in the study complained that the print size used in the PPI is too small. Furthermore, the study found that the surveyed people would appreciate a more detailed package leaflet [21].

A recent study carried out in Germany found that reading PPI might have less impact than assumed and that they are read selectively [22]. The authors concluded that personal recommendation from a physician or pharmacist is more helpful and more willingly accepted than information in PPI [22]. In the USA and Australia, pharmacy systems use computer-generated labels as a method of leaflet delivery. In contrast to package inserts, the computer-generated leaflets can be personalized and thus irrelevant information can be omitted and only age-specific information included, leading to a shorter but more relevant leaflet. Another major advantage of electronically generated leaflets is that they can be instantly updated. Introduction of a computerized system for labeling and dispensing of medications in Palestine would be beneficial, but that requires the introduction of automation and internet services to local community pharmacies beforehand.

In conclusion, there is a significant difference in the quantity and quality of information provided in the PPI of locally and imported anti-infective agents in Palestine. Experts in the Palestinian MOH need to review and approve the PPI content, to fulfill its role in health-care.

Table 1 Anti-infective agents available in the Palestinian market that was included in the study.

Anti-infective agent	Local products	Most popular imported equivalents
Amoxicillin	Amoxitid®, Moxypharm®, Amoxicare®	Moxypen®
Amox/ Clav	Ogmin®, Clamoxin®	Curam®
Azithromycin	Azimex®, Zitrocin®, Azicare®	Azenil®
Doxycycline	Doxypharm®, Doxal®, Doxacin®	Doxylin®
Trim/ Sulfa	Pathoprim®, Sulprim®, Sulfaprim®	Resprim®
Ofloxacin	Ultracin®, Taricin®	Oflodex ®
Cefuroxime	Zinex®, Zinaxim®	Zinnat®
Ciprofloxacin	Ciproxx®, Ciprocare®, Floxin®	Ciprofloxacin teva®
Cephalexin	Cefacare®, Cefalex®, Jeflex®	Keflex®
Metronidazole	Entogyl®, Metrozole®	Flagyl®
Fluconazole	Dican®, Flucan®	Trican®
Ketoconazole	Orazole®, Ketoral®	Nizoral®
Mebendazole	Vermacare®, Vermazole®	Vermox®
Clarithromycin	Klaricare®, Laricid®	Klacid®
Terbinafin	Lamirase®, Tanasil®	Lamisil®

Amox/Clav = amoxicillin/ clavulanic acid
Trim/Sulfa = Trimethoprim/sulfamethoxazole

Table 2 A and B: Word counts and statistical analysis

A. Word counts of the major eight headings in the patient package inserts of the locally produced and imported anti-infective agents

Variable		Description	Indications	Contraindications	Warnings	Drug Interaction	Dosage and Administration	Side effects	Storage	Total
Amoxicillin	Loc.	10.3	10.3	41.3	60.6	56	115.3	64	62.6	420.4
	Imp.	8	0	24	70	57	131	82	59	431
Amox/ Clav	Loc.	16	10.5	32.5	45.5	87	196	141.5	53.5	582.5
	Imp.	29	266	255	299	213	949	863	115	2989
Azithromycin	Loc.	7.3	29.7	16	53.3	61.7	118.7	87	43.6	417.3
	Imp.	6	13	39	32	54	105	68	72	389
Doxycyclin	Loc.	11	20.5	13	72.7	37.3	74	43.3	23.6	295.4
	Imp.	9	48	15	111	49	183	110	48	573
Trim/ Sulfa	Loc.	9.3	20.7	8	41.3	91.3	82.3	90.5	36.5	379.9
	Imp.	9	4	32	188	55	129	114	60	591
Ofloxacin	Loc.	6	32	21.5	46	53.5	43.5	63	22.5	288
	Imp.	6	40	65	123	122	198	439	47	1040
Cefuroxime	Loc	10.5	11.5	14.5	60.5	83.5	190.5	108	46	525
	Imp	22	190	7	241	77	292	307	4	1140
Ciprofloxacin	Loc.	11.3	14.5	26.5	91.3	56	103.3	54.3	34	391.2
	Imp.	13	31	33	171	63	185	106	57	659
Cephalexin	Loc.	8.6	12.3	9.7	82.3	53.3	137.3	55.3	49	407.8
	Imp.	227	175	14	584	0	318	155	44	1517
Metronidazole	Loc.	8	17	21.5	90.5	77.5	153	137	25.5	530
	Imp.	18	23	24	196	88	241	194	5	789
Fluconazole	Loc.	9	27	31.5	36.5	53.5	84.5	64.5	40.5	347
	Imp.	9	3	60	66	66	99	89	59	451
Ketoconazole	Loc.	6.5	6.5	10.5	85.5	65.5	77.5	85.5	40	377.5
	Imp.	6	9	53	133	76	83	114	52	526
Mebendazole	Loc	5.5	12	11	81	22	62.5	42.5	37.5	274
	Imp	6	0	23	63	43	269	58	50	512
Clarithromycin	Loc.	7.5	60	17	62	52	85	70.5	47.5	401.5
	Imp.	11	57	62	52	303	95	255	8	843
Terbinafin	Loc.	10	35.5	13.5	62	51	76.5	50.5	23	322
	Imp.	23	72	8	186	316	298	275	22	1200

B. Statistical difference between local and imported anti-infective agents for all products combined

Variable	Mean ± S.E of the total word count		P value
	Local agents	Imported agents	
Description	9.1±0.68	26.8±14.4	0.231
Indications	21.3±3.6	62.1±21.1	0.068
Contraindications	19.2±2.5	47.6±15.6	0.084
Warnings	64.7±4.7	167.7±35.6	0.008*
Drug Interaction	55.6±4.8	105.5±24.5	0.056
Dosage and Administration	104.2±12.3	238.3±54.8	0.024*
Side effects	74.8±8.1	215.2±53.9	0.016*
Storage	37.9±3.3	46.8±7.4	0.285
Total	386.8	903.3	0.010*

Table 3 Scores of the nine statements in the PPI of local and imported anti-infective agents used in the Palestinian market.

Anti- infective agent	Local	Imported
Amoxicillin	5	6
Amoxicillin/Clavulanic acid	5.5	8
Azithromycin	4.7	4
Doxycylin	3.3	5
Trimethoprim / Sulfamethoxazole	2.7	4
Ofloxacine	3.5	4
Cefuroxime	5	8
Ciprofloxacin	4	4
Cephalexine	4.7	5
Metronidazol	4.5	7
Fluconazol	4	5
Mebendazol	4	5
Clarithromycin	5	5
Terbinafin	4.5	7
Ketoconzole	5	4
Total scores	65.4	81

The score of each medication represents the number of statement in the PPI out of nine tested statements. Significant difference exists in the total scores between local and imported products. *P* value for difference of total score = 0.02. * Significant difference.

Table 4 Scores of the nine statements written in the leaflets inserted in the local and imported anti-infective agents.

Statements	**Local companies** **A** n = 4	**B** n = 8	**C** n = 10	**D** n = 14	**Total scores (local products)** n = 36	**Total scores (imported products)** n = 15
Inactive ingredient	0	0	0	0	0	6
Classification	1	7	10	9	27	11
Clinical pharmacology	0	0	0	0	0	4
Pregnancy, lactation	4	8	10	14	36	15
Overdose	2	7	5	14	28	15
Missed doses	1	6	7	13	27	9
Duration of therapy	0	8	6	14	28	15
Date of last revision	0	0	0	0	0	4
Not to use after expiry date	0	1	0	2	3	2
Total score	**8**	**37**	**38**	**66**	**149**	**81**
Maximal score	**36**	**72**	**90**	**784**	**324**	**135**
Percent score	**22.2%**	**51.4%**	**42.2%**	**8.4%**	**46%**	**60%**

The locally produced anti-infective agents are manufactured by four companies (A,B,C,D). The score represents number of statements written in the PPI. Percentage is calculated by dividing total score by the maximal score.

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