Assessment of prescribing information for generic drugs manufactured in the Middle East and marketed in Saudi Arabia

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BACKGROUND: Little research has assessed the quality of manufacturer-provided prescribing information or documented differences in key aspects of drug information among different marketed generic products of the same drug, particularly in the Middle East and Arabian Gulf. We assessed the quality of written prescribing information for selected generic drugs marketed in Saudi Arabia and manufactured in various countries of the Middle East.

METHODS: We assessed the correctness and completeness of information pertaining to indications, dosage, cautions/contraindications, side effects and drug interactions in 37 package inserts for generic products registered in Saudi Arabia and manufactured in the Middle East, including atenolol (6 inserts), fluoxetine (4 inserts), ciprofloxacin (11 inserts), metformin (7 inserts), and omeprazole (9 inserts). We also described deficiencies in the quality and quantity of manufacturer-provided information that could be misleading to patients and prescribers.

RESULTS: We found substantial disagreement in information between generic package inserts versus the British National Formulary and the package insert of the brand product marketed in Saudi Arabia. A cumulative average of 63±16% of drug information indicators were in agreement with these standard references. Section headings with the least conformity with study references were those related to dosage (57±28%) and side effects (54±30%).

CONCLUSION: Our results indicate that national authorities should implement appropriate measures aimed at removing misleading and incorrect information in generic package inserts and incorporating crucial prescribing information that is missing. National authorities in the Middle East and Arabian Gulf should strengthen collaboration and information interchange among each other and with international agencies to maintain common quality standards for delivering information through package inserts.

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Accepted for publication
April 2006

Ann Saudi Med 2006;26(3):192-199

Studies have shown that including an information leaflet in the drug package may help bridge the information gap between healthcare professionals and patients and improve patient knowledge about drugs.[1-4] Pharmacists and physicians also consider these inserts as handy references for drug information, especially when standard information resources are not accessible.[5] There is published data addressing drug information in general[6-9] and the readability of patient information provided in package inserts.[2,10-11] Very little research, however, especially in the Middle East and

Table 1. Number of drug information indicators for each of five selected drugs.

Drug	Indications	Dosage	Cautions/ Contraindications	Side Effects	Drug Interactions	Total
Atenolol	4	4	25	13	9	55
Ciprofloxacin	11	9	17	33	18	88
Fluoxetine	4	7	14	27	11	63
Metformin	3	2	10	5	12	32
Omeprazole	13	14	6	17	4	54

Arabian Gulf, has addressed the issue of documenting differences in key aspects of drug information among different marketed generic products of the same drug. In addition, little research has assessed the quality of manufacturer-provided prescribing information. Over 5500 pharmaceutical products are registered in the Kingdom of Saudi Arabia.[12] The Regulation of Registration Act, last amended in 1989, sets requirements for manufacturer package inserts of pharmaceutical products registered in the Kingdom.[13]

This report describes the methods and findings of an observational study that assessed the quality of written prescribing information for selected generic drugs that are marketed in Saudi Arabia and manufactured in various countries of the Middle East. The primary objective of this study was to assess the correctness and completeness of information pertaining to indications, dosage, cautions/contraindications, side effects and drug interactions presented in package inserts as compared to a world-renowned reference in drug information. Secondary objectives included pointing out the deficiencies in the quality and quantity of manufacturer-provided information that could be misleading to patients, patient caregivers and prescribers, as well as providing recommendations based on study observations to key regulatory agencies in Saudi Arabia.

Methods

Five drugs were selected for the study from among those meeting the following criteria: 1) the drug is widely used and well known, 2) has several indications, 3) has at least 4 generics registered in Saudi Arabia that are manufactured in the Middle East, 4) ranked in the top 30 drugs in terms of global sales in 2004 and 5) covered therapeutic areas of high worldwide relevance in terms of mortality and morbidity.[14] The selected drugs were atenolol, fluoxetine, ciprofloxacin, metformin and omeprazole.

Written information material, approved by the Saudi Ministry of Health and by the respective regulatory authorities of the countries of manufacture, were collected from pharmacies in Saudi Arabia in May 2005 for the different generics. Written materials were obtained in the form of package inserts prepared by the company holding the marketing authorization.

A total of 37 package inserts for generic products registered in Saudi Arabia and manufactured in the Middle East for atenolol (6 inserts), fluoxetine (4 inserts), ciprofloxacin(11 inserts), metformin(7 inserts), and omeprazole(9 inserts) were collected. Information contained under the following section headings: indications, dosage, cautions/contraindications, side effects, and drug interactions, was compared to that presented in the British National Formulary (BNF 49, March 2005) and the package insert of the brand product marketed in Saudi Arabia. The BNF was used as a reference as it has a worldwide reputation for being complete, independent, reliable, and practice-oriented as a source of drug information. Though not contemporary to the package inserts' publication dates, which ranged between 1996 and 2003, this recent BNF edition served the purpose of identifying requirements for updating prescribing information of products currently on the market. We developed a checklist for each drug, each of which had a varying number of drug information indicators: atenolol (55 indicators) ciprofloxacin (88 indicators), fluoxetine (63 indicators), metformin (32 indicators), and omeprazole (54 indicators) (Table 1). The drug information indicators, detailed in Table 2, were selected based on the presence of the information statements in both the BNF and brand product label. For the side effects section head-

Table 2. Detailed drug information indicators for five studied drugs based on statements in the British National Formulary (BNF) and brand package inserts.

Atenolol (55 indicators)
Indications and Dosage
Hypertension: 50 to 100 mg daily Angina pectoris: 100 mg daily or divided twice daily Arrhythmia: 50 to 100 mg daily Early intervention within 12 hours of myocardial infarction: intravenous over 5 minutes, 5 mg, then oral, 50 mg after 15 minutes, 50 mg after 12 hours, then 100 mg daily
Cautions
Renal impairment (moderate/severe): reduce dose; pregnancy: may cause intra-uterine growth restriction, neonatal hypoglycemia, and bradycardia; breast feeding: monitor infant, possible toxicity; stable/unstable heart failure/poor cardiac reserve; asthma; diabetes: modifies tachycardia of hypoglycemia; do not discontinue abruptly in patients with ischemic heart disease; risk of precipitating heart failure when beta-blockers and verapamil are used together in established ischemic heart disease; first-degree AV block; portal hypertension; history of obstructive airways disease; myasthenia gravis; history of hypersensitivity—may increase sensitivity to allergens; may reduce response to adrenaline; Prinzmetal's angina; masks signs of thyrotoxicosis
Contraindications
Uncontrolled heart failure; marked bradycardia; hypotension; sick sinus syndrome; second- or third- degree AV block; cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; pheochromocytoma (apart from specific use with alpha-blockers)
Side Effects
Bradycardia; deterioration of heart failure; postural hypotension; conduction disorders; bronchospasm; peripheral vasoconstriction; gastrointestinal effects; fatigue; sleep disturbances; rashes/dry eyes; nightmares/psychosis/ hallucinations; visual disturbances; exacerbation of psoriasis
Drug Interactions
Verapamil; diltiazem; nifedipine; digoxin; sympathomimetics; disopyramide; NSAIDs; anesthetics; clonidine

Ciprofloxacin (88 indicators)
Indications and Dosage
respiratory-tract infections: 250–750 mg twice daily Urinary-tract infections: 250–500 mg twice daily (100 mg twice daily for 3 days in acute uncomplicated cystitis in women) Chronic prostatitis: 500 mg twice daily for 28 days Gonorrhea: 250mg or 500 mg as a single dose Pseudomonal lower respiratory-tract infection in cystic fibrosis: 750 mg twice daily Child 5–17 years: up to 20 mg/kg twice daily (max. 1.5 g daily) Surgical prophylaxis: 750 mg 60–90 minutes before procedure Anthrax (treatment and post-exposure prophylaxis): 500 mg twice daily; child 30 mg/kg daily in 2 divided doses (max. 1g daily) Gastro-intestinal system (including typhoid fever) Bone and joint infection Skin infection Sepsis
Cautions
Epilepsy or conditions that predispose to seizures; G6PD deficiency; myasthenia gravis (risk of exacerbation); children or adolescents (arthropathy has developed in weight-bearing joints in young animals); tendon damage: tendon rupture may occur within 48 hours of starting treatment; elderly patients are more prone to tendinitis; the risk of tendon rupture is increased by the concomitant use of corticosteroids; if tendinitis is suspected discontinue immediately; exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs); avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria); renal impairment: moderate: half normal dose; pregnancy: avoid; breast-feeding: avoid—high concentrations in breast milk; discontinue if psychiatric, neurological or hypersensitivity reactions occur; may impair performance of skilled tasks (e.g. driving)
Contraindications
History of tendon disorders related to quinolones use; hypersensitivity
Side Effects
Dysphagia; tachycardia; edema; hot flushes; sweating; movement disorders; tinnitus; vasculitis; tenosynovitis; erythema nodosum; hemorrhagic bulla; hyperglycemia; gastrointestinal effects; antibiotic-associated colitis; Stevens-Johnson syndrome/toxic epidermal necrolysis; anorexia; increase in blood urea and creatinine; drowsiness; restlessness; asthenia; depression; hallucinations; photosensitivity; hypersensitivity reactions; blood disorders; disturbances in vision, taste, hearing and smell; angioedema; arthralgia/myalgia; tendon inflammation and damage; hemolytic anemia; renal failure; interstitial nephritis; hepatic dysfunction
Drug Interactions
Antacids; calcium salts; coumarins; dairy products; glibenclamide; iron; opioid analgesics; phenytoin; probenecid; sucralfate; theophylline; cyclosporine; NSAIDs; zolmitriptan; estrogens; didanosine; diazepam; metoclopramide

Fluoxetine (63 indicators)
Indications and Dosage
Depressive illness: 20-60 mg daily; (max. 80 mg daily) Bulimia nervosa: 60 mg daily Obsessive compulsive disorder: 20-60 mg daily Premenstrual dysphoric syndrome: 20 mg daily Child and adolescent<18: not recommended Discontinue if no improvement after 10 weeks

Cautions

Renal impairment: (moderate): give on alternate days (severe): avoid; reduce dose or avoid in severe liver disease; pregnancy: use only when required; breast-feeding: avoid; patients with epilepsy; history of mania; cardiac disease; weight loss; diabetes mellitus; risk of suicidal behavior with young adults; hemorrhage; impair performance of skilled tasks

Contraindications

Use during the panic phase; use with MAOI

Side Effect

Anorexia with weight loss; gastro-intestinal effects; hypersensitivity reactions/anaphylaxis; angioedema; arthralgia/myalgia; photosensitivity; nervousness/anxiety/insomnia; tremor; drowsiness; urinary retention; sweating; hyponatremia/inappropriate ADH secretion; hypomania/mania; movement disorders/dyskinesia; visual disturbance; hallucinations; convulsion; galactorrhea; sexual dysfunction; blood sugar change; fever; serotonin syndrome; abnormal bleeding/vaginal bleeding on withdrawal/GI hemorrhage; ecchymoses; blood dyscrasias: pancytopenia/thrombocytopenia/anemia; violent behavior; hair loss

Drug Interactions

Should not be started until 2 weeks after stopping a MAOI; warfarin/St. John's wort; tricyclic antidepressants; antiepileptics; lithium; serotonergics: sumatriptan, tramadol; tryptophan; electrocunvulsive therapy; flecainide; vinblastine; MAOI should not be started until at least 5 weeks after fluoxetine is stopped

Metformin (32 indicators)

Indications and Dosage

Diabetes mellitus; with insulin; with sulfonylureas
Initially 500 mg with breakfast x 1 week then 500 mg with breakfast/dinner x1 week then 500 mg with breakfast/lunch/dinner
Maximum dose: 3g divided three times daily

Caution

Measure serum creatinine before treatment and once or twice annually during treatment

Contraindications

Renal impairment: (mild) avoid due to increased risk of lactic acidosis; ketoacidosis; hepatic impairment: withdraw if tissue hypoxia likely; use of iodine-containing X-ray contrast media (do not restart metformin until renal function returns to normal); use of general anesthesia/surgery (suspend metformin 2 days beforehand and restart when renal function returns to normal); pregnancy: avoid and substitute insulin; breast feeding: avoid; heart failure; respiratory insufficiency

Side-effects

Anorexia; gastrointestinal side effects; metallic taste; rarely lactic acidosis (withdraw treatment); decreased vitamin-B12 absorption

Drug Interactions

Angiotensin-converting enzyme inhibitors; alcohol; anabolic steroids; antidepressants; antihistamines; beta-blockers; corticosteroids; diazoxide; diuretics; hormone antagonists; estrogens/progesterone; testosterone

Omeprazole (54 indicators)

Indications and dose

Adult
Benign duodenal ulcer: 20 mg daily x 4 weeks
Benign gastric ulcer: 20 mg daily x 8 weeks
Maximum dose: 40 mg daily
Ulcer Maintenance: 20 mg daily
Prevention of relapse in duodenal ulcer: 10 mg-20 mg daily
NSAID-associated ulcer treatment: 20 mg daily x 4-8weeks
NSAID-associated ulcer prophylaxis in patients with history of ulcer/dyspeptic syndrome): 20 mg daily
Zollinger-Ellison syndrome: Initial:60 mg daily; usual: 20-120 mg daily (>80 mg divide twice daily)
GERD Treatment: 20-40 mg daily x 4-8 weeks
GERD maintenance: 20 mg daily
Acid reflux disease -Reflux esophagitis (long-term management): 10-20 mg daily
Acid-related dyspepsia:10-20 mg daily x 2-4 weeks
H. Pylori: 20 mg twice daily or 40 mg daily x 1-2 weeks
Child >2 years
Severe ulcerating reflux esophagitis: 0.7-1.4 mg/kg daily x 4-12 weeks (max:40 mg daily)

Cautions

Liver disease: not more than 20 mg daily should be needed; pregnancy: toxicity in animal studies; lactation: avoid—no information available; may mask the symptoms of gastric cancer; presence of 'alarm features' (dyspepsia/bleeding/dysphagia/recurrent vomiting/weight loss); rule out gastric malignancy before treatment

Side Effects

Paresthesia; vertigo; alopecia; gynecomastia; stomatitis; encephalopathy in severe liver disease; hyponatremia; reversible confusion; agitation; hallucinations in the severely ill; increase the risk of gastro-intestinal infections; myalgia/arthralgia; skin reactions; gastro-intestinal disturbance; headache; dizziness; hematological: leucopenia/thrombocytopenia/agranulocytosis

Drug Interactions

Ketoconazole; diazepam; warfarin; phenytoin

ing, only those side effects that were frequent and severe were included. To be considered frequent, side effects had to be reported as appearing in at least 1% of patients, according to the American Hospital Formulary Service 2005.[15] To be considered severe, side effects had to fit the criteria published by the WHO Collaborating Center for International Drug Monitoring, Uppsala, Sweden.[16] Caution and contraindications section headings were combined under one entity in the statistical analysis. Statements found in the collected materials that were not documented in the BNF or brand package insert were disregarded from a statistical perspective, but incorrect statements are pointed out in the results and discussion sections. The statistical analysis was done in terms of frequencies.

Results

Results are expressed in terms of the percentage of correct indicators present in the package inserts compared to the number of indicators that should be present as per the BNF and brand product label (Table 3). The results indicate substantial disagreement in information between generic package inserts and the comparator references. A cumulative average of 63±16% of drug information indicators were found to be correctly stated in package inserts of the study generics. Section headings with the least conformity with BNF data were those related to dosage (57±28%) and side effects (54±30%). An average of 70±22%, 70±20% and 63±30% of drug information indicators pertaining to indications, cautions/contraindications and drug interactions, respectively, were correctly documented in the package inserts of study generics.

Particular deficiencies were noted in information related to doses in pediatrics and required dosage adjustments in patients with renal/liver impairment. Only two ciprofloxacin generics indicated the possibility of its use in children with cystic fibrosis and included the respective dosing. There was also inaccurate information pertaining to the dose range of fluoxetine in depression; in general, doses were not indication-specific (e.g., doses for bulimia and depression). Moreover, an incorrect maximum dose was indicated in one of the ciprofloxacin generics.

There were deficiencies in the indications section related to both the quantity and quality of written information. Out of 11 ciprofloxacin generics, only one stated anthrax infection as an indication. Only one metformin generic indicated the possibility of its use in combination with insulin. None of the omeprazole generics indicated use and dosage of the drug in severe ulcerating reflux esophagitis in pediatric patients. Certain generics contained indications that were not approved; these included hyperkinetic heart syndrome with atenolol and treatment of atypical mycobacterium with ciprofloxacin.

As for the cautions and contraindications section headings, certain cautions were stated under contraindications, and vice versa. This was observed in the ciprofloxacin package insert, where use in patients less than 18 years old was stated as a contraindication rather than a precaution. This may relate to the lack of updating of the prescribing information, which has been modified in recent years to utilize this drug in certain specific pediatric disease states (e.g. cystic fibrosis, anthrax infection) where benefits outweigh the risks of treatment. Moreover, recent safety data with regard to the risk of suicidal behaviour with fluoxetine was documented in only one of the reviewed package inserts. A serious drug interaction, metformin with contrast media, was not included in either the cautions or the drug interactions section of one of the metformin generics.

Of the package inserts reviewed in the study, only 60% indicated a publication date.

Discussion

An international comparative study analysed the variability in 78 written drug information materials in 26 different countries for three drugs.[17] The results showed substantial disagreement in the materials available to prescribers and patients in different countries. Disagreement was even found within a single country when written materials from different brands of the same drug were compared. The majority of the cases studied were related to products of the same mother company worldwide. That study suggested that there is an urgent need to increase information agreement between materials on drugs at the national level by measures such as requiring that prescribing information for all pharmaceutical equivalents be the same as that approved for a reference drug. A study conducted in Saudi Arabia in 1991 compared package inserts of 10 non-steroidal anti-inflammatory drugs marketed in Saudi Arabia by different companies with the US PDR reference. The

Table 3. Correctness and completion of information in generic package inserts vs. indicators based on the BNF and brand product label.[1]

Generic formulations	Indications (%)	Dosage (%)	Cautions (%)	Side Effects (%)	Drug Interactions (%)	Mean (%)	±SD	Company
Atenolol								
Canar	100	25	72	77	85	72	28	Tabuk
Glormin	100	100	80	66	100	89	16	Global Pharma
Hypoten	50	25	79	38	56	50	20	Hikma
Normoten	100	50	50	46	33	56	26	Al Jazeera
Tenol	100	100	58	85	89	86	17	Saudi-Kuwait
Tensotin	75	75	88	85	89	82	7	Julphar
Ciprofloxacin								
Ciflox	91	67	82	97	83	84	11	Saudi-Kuwait
Ciprocin	64	22	47	23	39	39	18	EPICO
Ciprodar	55	33	35	42	44	42	9	Dar Al Dawa
Ciproflacin	64	22	47	23	28	37	18	Ram Pharma
Ciproflox	64	44	41	42	22	43	15	Al Arabia
Ciprogen	91	89	53	87	56	75	19	Riyadh Pharma
Cipromax	73	33	35	94	28	53	29	Spimaco
Ciproxen	55	22	35	13	39	33	16	Jamjoom
Floxacin	73	33	65	35	61	53	18	SAJA
Quinox	64	44	29	35	56	46	14	Tabuk
Sarf	82	78	82	87	72	80	6	Julphar
Fluoxetine								
Evrex	100	85	75	37	45	68	27	Al Jazira
Flozak	100	71	88	44	73	75	21	Riyadh Pharma
Flutin	75	28	69	96	82	70	26	Julphar
Linz	75	71	69	37	64	63	15	Tabuk
Metformin								
Dialon	67	50	90	80	92	76	17	Julphar
Diaphage	67	50	80	100	75	74	18	UPM
Formit	67	50	80	80	8	57	30	Spimaco
Glucare	33	100	76	80	42	66	28	Al Jazira
Metaphage	33	100	60	40	33	53	28	Saudi-Kuwait
Metfor	33	50	70	20	42	43	19	Tabuk
Riyadhformin	100	100	100	60	25	77	34	Riyadh Pharma
Omeprazole								
Aciloc	69	71	67	87	100	79	14	Jamjoom
Gastrozole	62	64	83	33	100	68	25	Riyadh Pharma

Table 3. (continued). Correctness and completion of information in generic package inserts vs. indicators based on the BNF and brand product label.[1]

Generic formulations	Indications (%)	Dosage (%)	Cautions (%)	Side Effects (%)	Drug Interactions (%)	Mean (%)	±SD	Company
Hyposec	30	36	83	7	100	51	39	Ram Pharma
Omedar	38	21	83	40	100	56	33	Dar Al Dawa
Omeprex	46	29	83	13	100	54	36	SAJA
Omeral	92	93	100	33	100	84	29	Al Jazeera
Omiz	54	14	67	40	75	50	24	Tabuk
Oprazole	77	79	100	7	0	53	46	Hikma
Rizek	85	86	100	100	100	94	8	Julphar
Mean	70	57	70	54	63	63		
SD(+/-)	22	28	20	30	30	16		

SD= standard deviation.[1] Results calculated as % (observed number of correct indicators/actual number of indicators in Table 1)

comparison was based on the number of words, presence/absence of section headings, and other differences between the information in the package insert and the PDR as well as the Ministry of Health package insert requirements as required by the Registration Act in Saudi Arabia. The study showed variation in both the amount and type of information contained in Saudi-marketed products as compared with the US PDR. Moreover, section headings on possible adverse reactions or drug-drug interactions and the date of revision of the package insert were not mentioned in any of the Saudi-manufactured products.[5] Bjerrum et al[18] examined sources of inconsistency and diverging information in product information leaflets of different brands of generically identical drugs marketed in Denmark. Diverging information about indications for drug use, adverse effects, drug-drug interactions and precautions, as well as considerations concerning pregnancy and breast-feeding resulted in patient confusion, which may have lead to reduced compliance, as measured by the number of inquiries to pharmacies. The study concluded that initiatives should be taken to coordinate information in patient leaflets covering the same generic product.[18]

Another study conducted in Japan evaluated drug information in package inserts and interview forms according to necessity and importance for 324 generic drugs. Generics were found to have 25.3±18.7% to 46.1±14.2% of the information in the product labeling of brand name drugs when products were compared for quantity of information by formulation. Comparison according to manufacturer returned a larger range of variation, 14.4±8.6% to 64.3±14.2%. These data revealed that manufacturer differences play a large role in the provision of drug information. Generic drugs were found to have insufficient information on clinical data, pharmacokinetics, safety, side effects and non-clinical tests.[19]

Key observations in our study include the inaccuracy and incompleteness of the provided prescribing information in reviewed package inserts. The main reason is that information is outdated in many package inserts, especially for some that were initially published years ago (publication dates ranged between 1996 and 2003). This finding indicates the need to enforce requirements for regular updating of drug information in package inserts and to indicate the last revision date through an amendment of the Saudi Regulation of Registration Act to address these issues.

The incorrectness and lack of scientific reliability of the prescribing information, such as inappropriate doses or indications, is misleading to prescribers and pharmacists who consider package inserts as alternative references, especially in developing countries. Incompleteness of safety information whether it be side effects or cautions/contraindications is not acceptable. From a patient safety standing, the information should be complete to avoid any misadventures.

The correctness and completeness of information varied among manufacturers, with some being more consistent in presenting reliable in-

formation than others (Table 3). Accordingly, manufacturers should be notified of the need to improve the quality of their products' package inserts and upgrade the presentation of their data, and national authorities are urged to be proactive in this regard and implement standards.

This study, with its small sample size given the number of generics that have flooded the Saudi Arabian market, identifies key findings that may only be the tip of the iceberg. Our results indicate that national authorities should implement appropriate measures aimed at removing misleading and incorrect information in package inserts, which should be the same among generics, as well as incorporating crucial prescribing information, which was found to be missing. Package inserts should be rendered a reliable reference to promote patient safety and assist healthcare providers. Moreover, national authorities in the Middle East and Arabian Gulf should strengthen collaboration and information interchange among each other and with international agencies, such as the World Health Organization, to maintain common quality standards for delivering information through package inserts of generic products.

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