THE QUALITY OF DIFFERENT DICLOFENAC SODIUM TABLET FORMULATIONS SOLD IN PHARMACIES IN TANZANIA

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Abstract

Objective: The objective of this study was to investigate the possible reasons for decreased anti- inflammatory and analgesic activities in patients using generic diclofenac sodium tablet formulations (50mg) in Dar es Salaam.

Methodology: Different diclofenac sodium tablet products from different manufacturers were collected from twelve wholesale pharmacies with good storage conditions. In total 80 samples were collected, with a minimum of five samples from each wholesale pharmacy. In addition a survey on brands available and the pricing of different diclofenac formulations in 120 retail pharmacies was conducted. Analyses of the sampled tablet formulations were performed at the laboratory of Tanzania Food and Drug Athority. Both validated British and United States Pharmacopoeia methods were used to perform the analyses.

Results: On visual appearance of tablets, 18% of the collected samples had cracks and white patches on the coat. Same number of samples could not meet the requirements for drug content and disintegration rates respectively, whereas, 27 % failed the dissolution rate tests. Voltaren® (Norvatis Pharma, Switzerland), the originator's product was the most expensive, less available and a less bought product. Vivian® (Lincoln Pharma, India) and Dyclomax® (Medreich Laboratories, India) were sold cheapest and were available in all pharmacies including those in the peripheral part of the city.

Conclusion: Low anti- inflammatory and analgesic response reported by many patients with different pain conditions could be associated with the use of poor quality diclofenac sodium.

Key words: Diclofenac sodium tablets, quality assessment, pharmacological activity.

Introduction

Substandard and counterfeit drugs continue to be a major health burden in developing world.[1-11] Standards for quality of drugs are determined by their efficacy weighed against safety to health according to label claim, their conformity to specifications regarding identity, strength, purity, and other characteristics".[12] The use of faked or poor quality drugs can result in adverse clinical outcomes such as lack of effect, drug resistance, toxicity or side effects.[13-16]

Diclofenac is one of the non-steroidal anti-inflammatory drugs (NSAIDS) of the phenylacetic acid class. It has analgesic, anti-inflammatory and antipyretic activities and the drug is broadly used in different painful musculoskeletal conditions such as gout and arthritis. Diclofenac is used as potassium or sodium salt with the later being commonest in Tanzania.

The number of diclofenac tablet formulations found on the Tanzanian market, from different manufacturers has recently increased dramatically posing a quality concern. In Tanzania, diclofenac sodium is not "a prescription only medicine" drug and is sold over the counter. The drug is mostly available in tablet and injection formulations. However, there has been an increase in the number of complaints of individual patients experiencing no relief from pain and other musculoskeletal disorders after using various tablet brands of diclofenac sodium.

We suspected that the most probable reason for these low anti-inflammatory and analgesic responses among patients could be due to poor quality of diclofenac sodium tablet formulations. This work aimed at investigating the quality of generic diclofenac sodium tablet formulations marketed in Dar es Salaam.

Materials and method

Materials

Methanol, acetonitrile HPLC grade were obtained from BDH Limited, Poole, England. Other chemicals and reagents (analytical grade) were obtained from the same company. Diclofenac sodium reference standard was of analytical grade and was donated in kind by Unique Pharmaceutical Laboratories, Gujarat, 394116 Mumbai, India. Distilled water was produced at the TFDA quality control laboratory in Dar es Salaam and all analyses were carried in the same laboratory.

Instrumentation

The method applied a Merck-Hitachi liquid chromatograph equipped with a 20 µl loop (Villiers le Bel, France), Rheodyne sample injector (model 7725,Cotati, California, USA), a Merck-Hitachi UV/Vis detector (model L-42000, Tokyo, Japan), an L-6000 model high-pressure pump (Merck-Hitachi, Tokyo, Japan) and a chromato-integrator model D-2500 (Merck-Hitachi, Tokyo, Japan). A C-18 Hichrom® reversed-phase column 10 µm (25 cmx4.6mm I.D) purchased from Cambridge England was used.

A mobile phase described in the USP 24 was applied[17]. Disintegration and dissolution apparatus were Erweka (ZT 53) and Erweka (DT 70), respectively and were purchased from Germany. Disintegration (ZT 53) Erweka® GMBH, D-63150 Heusenstamm and dissolutions DT 70, Erweka® GmBH, D-63150, were from Germany. The dissolution apparatus was equipped with six wells and acidic as well as buffer dissolution media were applied.

UV spectrophotometer Cecil CE 3041 Cambridge, from England was used. Both acidic and buffer stages were measured spectrophotometrically at an absorbance of 276 nm using a 1-cm cuvet.

Sample collection

A list of diclofenac sodium tablet formulations registered in the country was obtained from Tanzania Food and Drug Authority (TFDA).

From each of the selected pharmacies, one sample of each brand of diclofenac sodium available was bought. The samples consisted of boxes containing ten blister packs of enteric-coated 50mg tablets. In total, eleven

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different brands were collected, altogether 80 enteric coated samples.

Each sample was coded and the name, strength, batch number, manufacturer's name and the expiry dates were recorded. The samples were sent to the quality control laboratory of TFDA in Dar es Salaam.

Wholesale pharmacies Selection

The samples were bought from 12 wholesale pharmacies with good storage conditions (good ventilation and cold chain) in order to rule out deterioration. A pre-collection survey was conducted so as to identify wholesale pharmacies with good storage conditions.

Only those tablet batches with a due long shelf-life (more than 6 months) were bought. All the sampled tablets were enteric coated. For pricing and availability surveys, 120 pharmacies were randomly selected from a list of pharmacies in Dar es Salaam and a structured questionnaire with open and closed ended questions was used. The questions focused on the source, the retail price of the product and the frequency at which the drug was bought by patients.

Sample analyses

Analyses of all samples were performed at the quality control laboratory of TFDA in Dar es Salaam. Validated methods were used for determination of dissolution rates and content of diclofenac in a tablet formulation[17, 18].

Physical tests

Physical tests included visual appearance of the tablets (the type of packaging, cracks, patches) and mean weight of the tablets.

Content determination

Content determination and dissolution tests of tablet samples were performed as indicated in the USP 24[17]. The analysis was conducted using 20 tablets from each batch and involved weighing, crashing into fine powder, extraction and measurements. The amount of diclofenac for dissolution was determined using uv spectrophotometric method [17] which was validated prior analysis of the collected tablet samples.

Disintegration rates and dissolution rate tests of enteric coated tablets

Disintegration rates of enteric coated sampled tablets were performed as indicated in the BP, 2000[18] which involves acid stage and buffer stage.

Dissolution was carried out using the spectrophotometric method described in the USP 2002 in which absorbances were measured at 276 nm. Dissolution tests were also performed in two stages: acid and buffer stages, the names "acid" or "buffer" bearing the nature of the medium used.

Results

Sources and prices of sampled diclofenac sodium formulation

Table 1 shows the sources of different brands of diclofenac sodium and their retail prices in Tshs per tablet (1 USD= Tshs 1200.00) found in Dar es Salaam retail pharmacies. Most of the samples on the market (58%) originated from India and their prices per tablet ranged between Tshs 20-60 with only Voltaren® being sold at Tshs 300-500/= per tablet. Vivian® and Dyclomax® were sold cheapest (Tshs 20.00 per tablet).

Table 1. The names of the products, countries of origin and price tablet in Tshs

Product	Country of origin	Unit price per tablet
Clofen-50®	India	30.00
Dyclomax®	England	20.00
Dicloran®	India	30.00
Diclo-50®	England	30.00
Diclofeanc	India	30.00
Diclo-Denk®	Germany	60.00
Rheumarene®	Egypt	50.00
Remethan®	Cyprus	40.00
Vivian®	India	20.00
Voltaren®	Switzerland	300.00
Elfenac®	Kenya	40.00

Physical appearance and labeling

All the tablets were blister-packed but white patches were detected on the surface of 8% of Clofen-50® tablets. Fifty six percent of the sampled Dyclomax® had cracked coat and the tablet surfaces were dull in appearance. All sampled tablets had a mean weight of 68±1.0 mg (results not shown).

Presence of diclofenac sodium in the sample formulations

The presence of diclofenac was verified by comparing its retention time with reference standard.

Content determination of an active component in tablet samples

USP demands that enteric-coated diclofenac sodium tablets should contain not less than 90.0% and not more than 105.0% of the active component. Based on this criterion, 18% (14/80) failed to meet the requirement for content of an active component (table 2). These products (Diclofenac from Medopharm India and Vivian®, Lincoln Pharm, India) were found to contain amounts below the pharmacopoeia limits.

Dissolution test

Acid stage

USP 24 requires that enteric coated diclofenac tablets should remain undissolved in the acidic medium. However, Dyclomax® and Vivian® tablets failed to meet this standard (table 3).

Table 2: Content of tablet formulations containing 50 mg Diclofenac sodium as label claim Pharmacopoeia requirement is for content is 95% - 105% of the active substance

Product	Mean amount mount found (mg)	% of the amount as per label claim	Remarks
Clofen®	48.9±0.5	97.8	Comply
Dyclomax®	49.7±1.2	99.4	Comply
Remethan®	47.7±0.5	95.4	Comply
Diclo-50®	49.9±1.0	99.8	Comply
Rheumarene®	49.2±1.1	98.4	Comply
Elfenac®	50.6±0.5	101.2	Comply
Dicloran	51.1±0.5	102.2	Comply
Diclo-Denk®	49.7±1.5	99.5	Comply
Voltaren®	47.9±0.5	95.8	Comply
Vivian®	39.0±1.8	78.0	Fail
Diclofenac	40.1±0.5	80.2	Fail

The disintegration test

The mean disintegration time of diclofenac sodium tablets should not exceed 60 minutes in the buffer medium and the tablets should not disintegrate in the acid medium.[18] All samples except Dyclomax® and Vivian® tablets passed the test. The results are shown in table 3. Dyclomax® and Vivian® disintegrated in an acid medium and did not disintegrated even after 60 minutes in the buffer medium contrary to BP requirements

Table 3. Disintegration and dissolution test results

Product	Disintegration time/ minutes	% released in 2 h (acid stage)	% released in 45 minutes (buffer stage)	Remarks
Clofen-50®	**20.17**	**0.24**	**91 ± 3.1**	**Comply**
Dyclomax®	**>> 60**	**24.0**	**53 ± 4.6**	**Fail**
Remethan®	**19.58**	**0.0**	**99 ± 3.6**	**Comply**
Diclo-50®	**24.40**	**0.2**	**82 ± 2.5**	**Comply**
Rheumarene®	**7.58**	**0.0**	**86 ± 2.1**	**Comply**
Elfenac®	**21.04**	**0.1**	**79 ± 2.0**	**Comply**
Dicloran	**21.40**	**0.0**	**78 ± 2.7**	**Comply**
Diclo-Denk®	**19.00**	**0.0**	**88 ± 1.5**	**Comply**
Voltaren®	**12.00**	**0.0**	**79 ± 3.1**	**Comply**
Vivian®	**>> 60**	**37.0**	**44 ± 3.1**	**Fail**
Diclofenac	**55.00**	**0.0**	**66 ± 4.4**	**Fail**

Buffer stage

The USP Pharmacopoeia 24 requires that the formulations should release not less than 70% of the labeled amount in 45 minutes in the buffer medium. Based on this criterion, 27% samples failed to meet the requirement. Among the failed products Vivian® (Lincoln Pharm, India) exhibited the lowest dissolution release (see table 3).

Discussion

This study has revealed the presence of some diclofenac sodium tablets brands (50mg) of poor quality. The presence of low content of active components has clinical implications. Indeed, low content of the active ingredient will lead to under-dosing the patient and consequently low therapeutic responses**.**

For enteric-coated tablets, dissolution is said to be satisfactory if not less than 70% of the label claim is released in the dissolution medium in 45 minutes.[17] In addition enteric-coated tablets should neither disintegrate nor show any crack in acidic media but should disintegrate in buffer media in not more than 60 minutes.[18] In this regard, 18% and 27% samples respectively failed the tests (table 3).

A maximum absorption of basic or acidic types of drugs requires an appropriate pH at the site of absorption. For a drug to be absorbed it must first disintegrate and dissolve for subsequent absorption to the intended site of the gastrointestinal tract (GIT). Disintegration is an indicator that the solid formulation will disintegrate and therefore be able to dissolve at the intended site of absorption and has got clinical importance especially in maximizing absorption. Low disintegration rates of Dyclomax® predicts low dissolution rates of the drug in the GIT.

On the other hand, failure of a drug formulation to meet the dissolution specifications is an indication that the formulation will pass through the GIT unabsorbed[19] In this regard, three diclofenac products from India showed low dissolution rate in a buffer stage, predicting low drug bioavailability.

Maintaining good storage conditions of enteric- and sugar- coated tablets in most of pharmacies and medical stores found in resource limited countries could be an issue and this contributes to hardening of the formulation and subsequently poor disintegration and dissolution [19]. In our case, all diclofenac formulations tested were collected from wholesale pharmacies with good drug storage conditions therefore any discrepancy in the drug quality could be associated with poor manufacturing practice. Enteric-coated formulations seem to pose a great technological challenge in many pharmaceutical industries based in developing countries.[20] Rimoy et al also observed low dissolution parameters and low bioavailability of sugar-coated chloroquine tablets formulation marketed in East African countries.[21]

The cheapest and frequently used diclofenac sodium formulation (Dyclomax® and Vivian®) failed to meet the standards for content, disintegration and dissolution, suggesting that patients who used this formulation were exposed to sub-therapeutic levels, thus lack of pain relief.

Availability of poor quality diclofenac tablets in wholesale pharmacies is a reflection of distribution of substandard drugs to dispensaries, retail pharmacies and medical stores where patients seek medical care.

Quality assurance of drugs requires a well equipped analytical laboratory and well trained personnel which is still an anecdote in most resource limited countries. The Tanzania Food and Drug Agency, which is the drug regulatory authority in the country is on the verge of improving its performance through collaboration with the Drug analysis experts at Muhimbili University College of Health Sciences and already it has a well functioning analytical laboratory which would require more capacity building.

Conclusion

This study has confirmed the presence of poor quality of diclofenac sodium tablet formulations on the pharmaceutical market of Tanzania. Poor responses in treating various musculo-skeletal disorders as reported by

individual patients could be associated with use of poor quality diclofenac tablet formulations.

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