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Quality Of Sulfadoxine/Pyrimethamine Tablets Marketed In Dar Es Salaam, Tanzania

M. B. JANDE[1*], O. NGASSAPA[2] AND I. O. KIBWAGE[3]

[1]*Department of Clinical Pharmacology, Faculty of Medicine, Muhimbili University College of Health Sciences, P.O. Box 65010, Dar es Salaam, Tanzania.*
[2]*Department of Pharmacognosy, Faculty of Pharmacy, Muhimbili University College of Health sciences, P.O. Box 65013, Dar es Salaam, Tanzania.*
[3]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Nairobi, P.O. Box 19676, Nairobi, Kenya.*

The quality of brands of Sulfadoxine/pyrimethamine tablets, from nine different manufacturers, was assessed, by determining the content of active ingredients and their dissolution profile. All nine brands complied with the USP requirement for the content of sulfadoxine and pyrimethamine. However, only four brands passed the dissolution test, which according to the USP, requires that more than 60% of each active ingredient should be in solution in 30 minutes. One brand failed the dissolution test, with respect to both active ingredients, for which only 19.9% and 56.9% of pyrimethamine and sulfadoxine, respectively, were in solution, in 30 minutes. The remaining four brands, failed with respect to pyrimethamine, for which less than 60% was in solution in 30 minutes. These findings clearly indicate that, in addition to parasite resistance to sulfadoxine/ pyrimethamine, failure of this drug combination to cure malaria could also be due to the sub-standard products available on the market. It is recommended that pharmaceutical manufacturers should ensure that their products meet the required standards by adherence to good manufacturing practice. Statutory drug control bodies should also ensure that each product, imported or locally manufactured, meets the required compendial standards before being permitted to be on the market.

Key words: Sulfadoxine/Pyrimethamine, quality assurance, Dar es Salaam, Tanzania.

INTRODUCTION

Chloroquine and amodiaquine, both 4-aminoquinolines have long been the drugs of choice for treating uncomplicated falciparum malaria in Africa, but resistance to them is now common and increasing. Sulfadoxine/ pyrimethamine (SP) has been suggested as an alternative when the 4-aminoquinoline treatment fails. In Malawi, for example, sulfadoxine/ pyrimethamine replaced chloroquine, in 1993, as the first line drug for acute uncomplicated malaria [1]. The same combination was proposed for consideration to be a first-line drug for malaria in Northern Kenya, since parasitological resistance to chloroquine in the area was found to be significantly high [2].

Resistance to SP has been reported, both in Africa and Asia [3 – 7]. Although SP failures in malaria are usually due to drug resistance, the use of SP preparations of poor quality could also be a contributing factor. Marketing of drugs of poor quality is a major concern in most developing countries and has been widely reported in Africa and elsewhere [8 – 11]. This study was carried out in order to assess some of the important parameters in the quality of solid dosage forms, such as tablets. This paper, reports on findings of the determination of content of active ingredients and dissolution tests carried out on nine brands of SP tablets marketed in Dar es Salaam, Tanzania.

Dissolution test measures the proportion of active ingredient dissolved within a stated period of time under specified standard *in vitro* conditions. However, it does not, exactly, mimic the *in vivo* condition. This is a very important quality control measure for all solid dosage forms, since before a

* Author to whom correspondence may be addressed.

drug is absorbed it must first dissolve in the gastro-intestinal tract fluid. Every oral solid dosage preparation must have satisfactory dissolution characteristics to be therapeutically effective.

EXPERIMENTAL

Drug samples, reagents, solvents and mobile phase

Nine brands of sulfadoxine/pyrimethamine tablets from various manufacturers were purchased from various pharmacies in Dar es Salaam, Tanzania. Eight brands were imported into the country, one was locally manufactured. The brands and manufacturers are listed in Table 1.

Potassium dihydrogen phosphate and potassium hydrogen phosphate (Across Organics, New Jersey, USA), acetonitrile and glacial acetic acid (Fisher Scientific, UK) were all of analytical grade. The mobile phase consisted of water/ acetonitrile/acetic acid/0.1 M potassium dihydrogen phosphate buffer (69:20:1:10) volume parts.

Liquid chromatographic (LC) analysis

The liquid chromatographic system consisted of a model 305 solvent delivery system, and a model 115 spectrophotometer detector set at 254 nm (Gilson, Paris, France), coupled to a model HP 39363 integrating recorder (Hewlett Packard), and a model CV-6-UHPa-H60 sample injection valve (Valco, Houston, TX, USA) equipped with a 25μm loop. The column (250 x 4.6 mm id) was laboratory packed with RSil C_{18}HL, 10 μm (BioRad, Eke, Belgium) and was maintained at 40° C by immersion in a water bath.

Table 1: Brands of Sulfadoxine/Pyrimethamine Tablets and Manufacturers

Ser. No.	Brand name	Manufacturer & Country
1.	Falcidin^R	Cosmos LTD, Kenya
2.	Fansidar^R	F. Hoffmann La Roche LTD., Switzerland
3.	Fansimax^R	Mac's Pharmaceuticals LTD, Kenya
4.	L-Kelfin^R	Lincoln Pharmaceuticals, India
5.	Malodar^R	Laboratory and Allied, Kenya LTD, Kenya
6.	Malostat^R	Intas Pharmaceuticals LTD, India
7.	Orodar^R	Elys Chemical Industries LTD, Kenya
8.	Paludar-Z^R	Aurochem Laboratories and PTIE LTD, India
9.	Sulphadar^R	Shelys Pharmaceuticals LTD, Tanzania

Preparation of samples for analysis

Internal standard solution: This was prepared to a concentration of caffeine 1 mg/ml in methanol.

Standard solution: 31.25 mg of pyrimethamine was transferred to a 25ml volumetric flask and dissolved and made up to volume with methanol. Sulfadoxine was weighed (25 mg) into a 50 ml volumetric flask and dissolved in 20 ml acetonitrile. To this solution 1.0 ml of the pyrimethamine solution was added and the solution made to volume with the mobile phase. Then 9.0 ml of this solution was mixed with 1.0 ml of internal standard and injected into the column.

Sample solution: A powder, equivalent to 125 mg of pyrimethamine was transferred to a 25ml volumetric flask. Then 5 ml of methanol and 10 ml of acetonitrile were added, and the mixture was sonicated for 5 minutes. The mixture was made up to volume with the mobile phase and filtered through a 0.45 μm membrane filter. Then 1.0 ml of the solution was diluted to 10.0 ml with the mobile phase. Nine ml of the resulting solution was mixed with 1.0 ml of internal standard and injected onto the column.

Dissolution study

Dissolution profile was determined following the USP paddle method [12] with 0.05M potassium phosphate buffer, pH 6.8 as the dissolution

medium. Samples of 10ml aliquots were withdrawn from the dissolution medium and replaced with a similar volume of fresh medium. Sampling times were 10, 30, and 60 minutes. The withdrawn sample was filtered through a 0.45μm membrane filter. Then 9.0 ml of the filtrate was taken, mixed with 1.0 ml of internal standard and injected onto the column.

RESULTS

All nine brands of sulfadoxine/pyrimethamine tablets complied with the USP 1995 [12] requirements for the content of active ingredients, which should be not less than 90% and not more than 110%, for both sulfadoxine and pyrimethamine (see Table 2).

With respect to the dissolution test, only four brands (A, C, G and H) met the USP standards for both active ingredients, which require that at least 60% (Q) of each active ingredient should be in solution within 30 minutes (Table 3). One brand, B, failed the dissolution test with respect to both active ingredients. At 30 minutes, only 19.9% of pyrimethamine and 56.9% of sulfadoxine were in solution. In the remaining four brands (D, E, F and I), only the pyrimethamine component failed the dissolution test. The amount of pyrimethamine, which was in solution after 30 minutes, was 31% for D, 23.3% for E, 49.3% for F and 24.8% for I.

Table 2: Chemical content of various Sulfadoxine/Pyrimethamine brands

Brand	Manufacture date	Expiry date	Sulfadoxine content (%)	Pyrimethamine content (%)
A	Nov., 1997	Oct., 2000	102.70 ± 0.98	98.80 ± 0.60
B	Mar., 1998	Sept., 2001	94.50 ± 0.50	97.80 ± 1.40
C	June, 1996	June, 2001	99.00 ± 0.36	98.90 ± 0.26
D	Feb., 1998	Jan., 2001	100.90 ± 1.40	102.20 ± 0.08
E	Dec., 1997	Nov., 2001	98.00 ± 0.61	98.10 ± 1.35
F	-[a]	-	96.50 ± 1.10	104.70 ± 1.20
G	-	June, 2001	100.20 ± 1.45	103.50 ± 0.78
H	-	Mar., 2002	99.30 ± 0.98	99.10 ± 0.60
I	Jul., 1997	June, 2000	98.40 ± 0.72	97.90 ± 0.41

-[a] no date was indicated on the label

TABLE 3: Dissolution profile of various brands of Sulfadoxine/Pyrimethamine

Brand	Mean % in solution at 15 min		Mean % in solution at 30 min		Mean % in solution at 45 min		Mean % in solutin at 60 min	
	SDX	PMT	SDX	PMT	SDX	PMT	SDX	PMT
A	71.10 (± 4.18)	55.86 (± 3.05)	95.06 (± 2.21)	71.60 (± 4.49)	97.68 (± 1.37)	76.30 (± 3.64)	98.65 (± 1.49)	79.30 (± 3.40)
B	44.90 (± 2.62)	14.54 (± 1.69)	56.87 (± 3.39)	19.86 (± 0.99)	63.86 (± 1.95)	25.95 (± 0.82)	70.01 (± 1.86)	31.20 (± 1.40)
C	76.78 (± 4.87)	69.40 (± 3.20)	87.30 (± 3.70)	82.80 (± 3.90)	90.50 (± 4.30)	93.50 (± 4.50)	93.90 (± 2.80)	96.50 (± 4.20)
D	77.13 (± 4.68)	21.90 (± 2.40)	83.60 (± 4.99)	31.03 (± 3.01)	90.00 (± 7.96)	39.82 (± 3.93)	92.70 (± 8.14)	47.30 (± 5.79)
E	61.77 (± 2.00)	17.00 (± 1.01)	78.77 (± 4.42)	23.30 (± 2.24)	90.10 (± 3.88)	36.05 (± 3.81)	93.84 (± 3.83)	41.99 (± 3.59)
F	75.45 (± 3.02)	39.35 (± 1.93)	81.86 (± 1.82)	49.35 (± 3.27)	82.84 (± 2.08)	55.65 (± 5.13)	83.13 (± 2.32)	60.30 (± 1.91)
G	86.60 (± 3.40)	58.10 (± 4.60)	91.80 (± 3.90)	70.90 (± 4.50)	92.70 (± 1.60)	75.70 (± 3.20)	93.80 (± 2.70)	82.50 (± 4.70)
H	73.94 (± 3.95)	61.99 (± 5.17)	91.26 (± 3.07)	74.58 (± 1.05)	94.95 (± 1.05)	76.73 (± 2.00)	98.50 (± 1.65)	78.53 (± 1.49)
I	58.95 (± 2.36)	14.70 (± 1.32)	79.88 (± 4.73)	24.76 (± 3.83)	90.18 (± 3.49)	31.58 (± 3.73)	93.66 (± 3.29)	36.02 (± 4.85)

SDX = Sulfadoxine, PMT = Pyrimethamine

DISCUSSION

The present study has shown that some sulfadoxine/pyrimethamine brands, both locally manufactured and imported, did not meet the required standard, for the dissolution test, particularly for pyrimethamine. Failure of pyrimethamine to comply with compendial requirements for dissolution could, partly, be due to its poor solubility characteristics in aqueous media. However, it is the duty of manufacturers to ensure that their products are properly formulated, so as to meet the required standards and be effective. Previous analytical studies done on chloroquine preparations marketed in Tanzania [13] and Co-trimoxazole preparations marketed in Kenya [14] revealed a number of products, which were of poor quality. Both drugs are widely used for the management of malaria in Tanzania [15]. With the increasing chloroquine resistance, it has been suggested that sulfadoxine/pyrimethamine combination should now be the drug of first choice for the treatment of acute uncomplicated malaria attacks. But, with so many poor quality brands in the market, one wonders what will be the impact clinically, when such brands are taken by patients. A randomized control study on the bioavailability of such brands would be able to substantiate this.

Previous studies have shown that treatment failure with sulfadoxine/pyrimethamine could be due to malaria parasite dihydrofolate reductase mutation [16] or dihydropteroate synthetase mutation [17], but also poor quality could be a contributing factor. Drug dissolution is an important determinant of bioavailability. For preparations showing low dissolution rate at 30 minutes, only one (F) had 60% of its pyrimethamine content in solution when the time was increased to one hour. Such poor dissolution characteristics will definitely affect the bioavailability of such products and the clinical outcome.

A bioavailability study done in Kenya on two oral preparations of sulfadoxine/pyrimethamine, one of which was Fansidar^R from Roche Pharmaceuticals, revealed that the products had good bioavailability characteristics, with no significant difference between them [18].

Fansidar^R tablets from the same manufacturer, analyzed in this study, have also been found to be of good quality. The product complied with the USP requirements for both, the content of active ingredients and the dissolution test. It is recommended that bioavailability studies should also be carried out in Tanzania, particularly, for brands, which failed the dissolution test.

In conclusion, we suggest that manufacturers should adhere to good manufacturing practice and have good quality control, while statutory control bodies should enforce high quality standards and check on every product in the market, in a randomized manner.

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