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Short Communication

Comparative Bioequivalence Assessment of Aspirin Tablets Marketed in Nigeria

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Abstract

Purpose: In the last few years, aspirin has become a life saver against cardiovascular accidents. This investigation was carried out to determine possible bioequivalence between regular aspirin and soluble aspirin tablets marketed in Nigeria.
Methods: The in vivo bioavailability profiles of three commercial brands of aspirin tablets and soluble aspirin tablets were assessed in eight healthy subjects. Pharmacokinetic parameters including amounts of aspirin excreted up to 24h (E_{24h}), maximum excretion rate $(dE/dt)_{max}$ and time for maximum excretion rate (T_{max}) were compared for all the brands.
Results: There was no significant difference ($p > 0.05$) in the maximum excretion rates among all the brands but the amount of soluble aspirin excreted up to 24 hours was a significantly different ($p < 0.05$) from one of the regular brands of aspirin. The soluble brand had significantly lower T_{max} ($p < 0.05$) than all the three plain brands. There was no significant inter-subject variation among the subjects that participated in the study.
Conclusion: Bioinequivalence exists between some regular aspirin and soluble aspirin marketed in Nigeria.

Keywords: Soluble aspirin, aspirin, pharmacokinetic parameters, in vivo bioequivalence

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Introduction

After almost a century of clinical use, aspirin (acetylsalicylic acid, ASA) still remains one of the world's most extensively used drugs. Its analgesic and antipyretic effects have been recognized for more than 200 years. Since late 1890s, it has been used to treat a variety of inflammatory conditions. The antiplatelet activity of this agent was not recognized until almost 70 years later [1-3]. It has poor water solubility and its dissolution rate is the rate limiting step affecting its bioavailability – the rate and extent of absorption [4].

Aspirin is rapidly and extensively absorbed by first-order kinetics and distributed through out the body fluids. Following oral administration, it is rapidly metabolized and excreted as salicylate. Because of its rapid conversion to salicylate, its concentrations in both the plasma and urine decline within a short period while that of salicylate increases and maintained for a long time thereby making the assessment of salicylate a good parameter for assessing aspirin bioavailability [5,6]. Many factors such as drug formulation, rate of gastric emptying, volume of blood, concurrent administration of other drugs, posture, exercise and pH of stomach content affect the rate and extent of absorption of the drug [7,8].

There are different plain and soluble brands of aspirin tablets readily in use in Nigeria as over- the- counter (OTC) drugs. Soluble aspirin tablets usually contain calcium carbonate as buffer in their formulations which enhances its dissolution and absorption. In vivo bioavailability requirement has become an essential parameter in quality control of a number of medicinal products particularly; those which have low or high therapeutic indices or those which are poorly water soluble [9,10]. Both bioequivalence and bioinequivalence of aspirin have been reported in various studies [4-6,11,12]. However, the lack of adequate bioequivalence data as regards plain and soluble brands of aspirin marketed in Nigeria necessitated this study.

Experimental

Materials

The following chemicals were used as procured from their local suppliers: sodium salicylate (BDH, England), ferric ammonium sulphate (May and Baker, Nigeria), chloroform, hydrochloric acid (May and Baker, England). Four commercial brands of aspirin 300 mg tablets from various manufacturers were purchased from a retail pharmacy outlet in Jos, Nigeria.

The soluble brand was labeled A1 while the other three plain brands were labeled A2 - A4. They were within their expiry dates. The primary and secondary packages were well examined to ensure physical integrity of the products.

Study Design

Eight healthy adult volunteers (4 males and 4 females; age, 18-29 yr; weight, 50-68 kg; height, 1.53-1.71 m) that had no history of liver, kidney or gastro intestinal disease participated in the study. They did not take any medication, alcohol, and other beverages or food that might interfere with the drugs, one week prior and throughout the entire study period. Ethical Clearance was obtained from the Institution's Research Ethics Committee before the start of the study and the study followed the stipulated Committee Guidelines on Conduct of Human Experiments.

The study was carried out using a random cross-over design, with 7 days interval between administrations of each formulation as the washout period. Following an overnight fast, each subject was asked to void his/her bladder and drink 250 ml of water. After 1 hr, two tablets of aspirin (600 mg) were ingested with 250 ml of water. No food or liquid other than water were permitted for over 4 hr, following ingestion of the dose. Cumulative urine samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hr. The volume of the urine samples collected was measured at each collection time. Aliquot of the urine samples were stored at 4 °C immediately and protected from light. Each subject was instructed to drink 250 ml of water after each urine sample collection for the first 3 hr and a uniform meal was served after the 4-hr sampling.

Determination of salicylate excreted in urine

The total amount of salicylate in the urine sample was measured using the procedure of Chio and Onyemelukwe [13]. A 2 ml volume of concentrated hydrochloric acid was added to 3 ml of urine samples in a screw top Pyrex culture tubes. After sealing the tubes with caps, they were incubated in a hot air oven at 100 °C for 17 h. After cooling to room temperature, 0.5 ml of 5 N HCl and 6 ml of chloroform were added to the tubes, shaken mechanically for 10 min and centrifuged for 5 min using a centrifuge (Cliffton Kickel Elctron Limited, England). The clorofom layer (3 ml) was then accurately transferred to another screw-top culture tube. A 6 ml of modified Trinder's reagent was added and the tubes were shaken for 10 min and centrifuged again for 5 min. The absorbance of the aqueous layer was then measured at 540 nm using a UV spectrophotometer (Spectronic 21, Milton Roy Company, USA) and the modified Trinder's reagent for 100% transmittance adjustment. The concentrations of salicylate excreted in the urine samples were then determined from a calibration curve as previously reported [5,6].

Data analysis

Pharmacokinetic parameters determined were cumulative amount excreted up to 24h (E_{24h}), maximum excretion rate $(dE/dt)_{max}$ and time for maximum excretion rate (T_{max}) were determined directly as previously reported [13]. The parameters for the soluble aspirin were each compared with those of the other three brands of plain aspirin using multiple comparison to establish any bioequivalence [14]. At 95% confidence interval, 2 tailed p values less than 0.05 were considered significant.

Results

The salicylate excretion profile of the soluble aspirin and the plain aspirin tablets are presented in Figure 1 and the pharmacokinetic parameters are provided in Table 1.

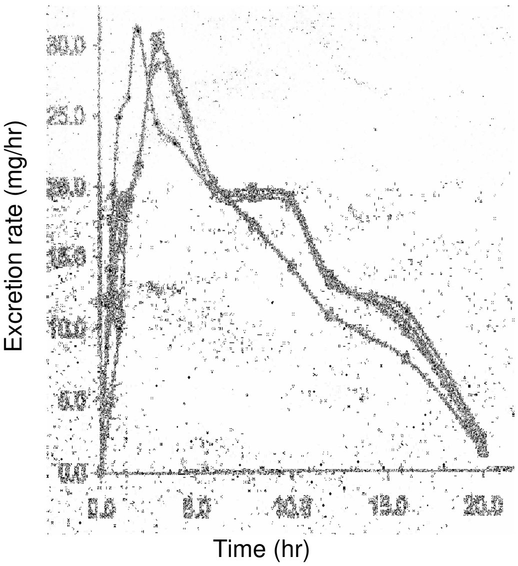

Figure 1: Excretion rate profiles of soluble aspirin (♦) and three different plain aspirin (A_2, ■; A_3, ▲; and A_4, ^) tablets

It was observed that there were similarities in the profiles of total cumulative amount of salicylate excreted up to 24 hours (E_{24h}) for all the different brands of aspirin. However, significant difference between the soluble aspirin brand and the other brands were observed in the T_{max} ($p<0.035$). The cumulative amount of salicylate excreted in 24h for one of the brands of plain aspirin tablets was significantly different from that of the soluble brand of aspirin ($p=0.043$).

Table 1: Pharmacokinetic parameters of soluble and plain aspirin tablets in 8 healthy volunteers

Parameters	Soluble Aspirin	Plain Aspirin			P – Value*		
	A_1	A_2	A_3	A_4	A_2	A_3	A_4
T_{max} (hr)	2.50	3.38	3.50	3.13	0.004	0.001	0.033
$(dE/dt)_{max}$ mg/hr)	32.76	29.93	29.64	31.36	0.434	0.39	0.698
E_{24h} (mg)	290.59	275.68	247.63	281.10	0.468	0.043	0.643

**Comparative data with those of soluble aspirin*

Discussion

This study has demonstrated the possible differences between the pharmacokinetics of plain aspirin tablets and the soluble brands as the T_{max} of the different brands of plain aspirin tablets were significantly different from that of the soluble brand of aspirin. We are certain that the method employed for the assay was good enough as colorimetric assay has been widely used in the assessment of salicylate level both in the plasma and urine [11-13,15].

Soluble aspirin is usually formulated to contain calcium carbonate as a buffer which can provide a reactive medium that changes the pH of the environment adjacent to the drug to alkaline, thus making the aspirin (a weak acid) to form a water soluble salt. This enhances the rapid dissolution and absorption of aspirin [7,16,17].

Conclusion

Based on the significant statistical difference between the T_{max} of A1 and all the other brands A2 - A4, this study suggests that the three plain brands of aspirin tablet are not bioequivalent to the soluble brand of aspirin and might not be considered therapeutically equivalent or interchangeable based on pharmacokinetics effects.

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