Urinary Excretion and Renal Clearance of Nimesulide in Male Volunteers

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Abstract

Drugs are eliminated from the body either unchanged as the parent drug or as metabolites. Nimesulide drug belongs to a wide class of medicines called antiinflammatory nonsteroidal drugs (NSAID). NSAIDs are well known for their antipyretic, anti-inflammatory, and analgesic properties. Renal clearance of nimesulide correlated with creatinine clearance. The present research work was planed to determine urinary excretion and renal clearance of nimesulide after its oral administration. Blood and urine samples of the human male volunteers (n=10), after the oral administration of drug, were collected at predetermined time intervals. The concentration of the nimesulide in urine and plasma of male volunteers was determined by HPLC. Statistical analysis was performed in order to determine the significance of the results.

Index terms—

1 Introduction

he body begins to eliminate the drug by hepatic metabolism, renal or both, after administration of the dose. The renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidney per unit time. The kidneys are the primary means for elimination waste products of metabolism that are no longer needed by the body. These products include urea, creatinine, uric acid and end products of haemoglobin breakdown and metabolites of various hormones. These waste products must be eliminated from the body as rapidly as they are produced. The kidneys also eliminate most toxins and other foreign substances that are either produced by the body or ingested, such as pesticides, drugs and food additives (Guyton and Hall, 2000).

Kidney, skin, lung, gastrointestinal tract, salivary glands and liver are the main channel through which excretion takes place. Among the main channel of excretion, kidneys are chief. Kidneys are the major organ of homeostasis, preventing alternation in volume osmolatity, ionic composition and pH of body fluids **??**Bander and Pugh, 1977). and extensively after received oral nimesulide 100 mg (tablet, granule or suspension form) in healthy volunteers (Bernareggi, 1998).

Nimesulide; a relatively COX-2 selective, nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties; is approved for the treatment of acute pain, osteoarthritis and primary dysmenorrhoea in adolescents (Rosalinde and Russel, 2010). Nonsteroidal anti-inflammatory drugs (NSAIDs) are the group most often used in human health care, since they are available without prescription for treatment of fever and minor pain **??**Starek and Krzek, 2009).

Excretion of nimesulide metabolites in the urine and feces account for about 80% and 20% of the administered dose, respectively (Yesilot et al.2010). Nimesulide rapidly and effectively provides relief of pain and the signs and symptoms of inflammation associated with a wide array of disorders. Nimesulide has especially proved useful in patients who do not respond adequately to other NSAIDs, and in patients who are NSAID-intolerant due to hypersensitivity (e.g., asthmatics) or gastric intolerance. The body defends itself against potentially harmful compounds like drugs, toxic compounds and their metabolites by elimination in which the kidney plays an important role (Silva et al 2010). Renal clearance is used to determine renal elimination mechanisms of a drug, which is the result of glomerular filteration, active tubular secretion and reabsorption. The renal proximal

tubule is the primaty site of carrier-mediated transport from blood to urine. Renal secretory mechanisms exists for, anionc compounds and organic cations (Rosalinde and Russel, 2010).

2 II.

3 Aims and Objectives

To study the urinary excretion and renal clearance of nimsulide by using HPLC in female volunteers after oral administration.

4 III.

5 Material and Method

This study was conducted to analyze the urinary excretion and renal clearance of nimesulide and endogenous creatinine in blood and urine. samples of healthy male volunteers after the oral administration of 100 mg nimesulide were collected. The experiments were conducted on 10 male volunteers. The main responsibility for adjusting the solute and water excretion is borne by the kidney **??**Tadlock, 1993).

Nimesulide is extensively bound to albumin; the unbound fraction in plasma was 1%. The unbound fraction increased to 2 and 4% in patients with renal or hepatic insufficiency. The drug was absorbed rapidly IV.

6 Volunteers

The healthy male volunteers choose for this study was the students of University of Agriculture Faisalabad. Each volunteer was apprised of design for this research work. The volunteers who willing offered to participate were included in this study, The volunteers choose for this study are physically fit and their previous medical history shows that They were never found any serious disease. The complete demographic data of each volunteer is described in the table 3.1

Blank blood and urine samples were taken from each volunteer then the each volunteer was given 100 mg tablet of nimesulide (Sami industries) orally. The age body weight' height, blood pressure and body temperature of volunteers were recoded and presented in Tablet 3.1. Volunteers were offered similar breakfast after one hour of the drug administration.

V.

7 Drug Administration

The drug nimesulide 100 mg of (Sami industries Pakistan limited Karachi) was given to each of the participate in this study. The drug is given orally with the glass of water. The samples for the analysis were collected in the month of (June 2011) and the samples stored at -20?C temperature until analysis.

8 Table 3.1 : Deamographic data of male volunteers

9 Sampling procedure; a) Collection of blood samples

Before the drug administration blank blood samples were collected from each volunteer. The blood samples of each volunteers were collected after 1 and 3 hours. After the oral intake of nimesulide 100mg (Sami industries Pakistan Karachi) these blood samples were stored in ependorf tubes at -20?C until use for the analysis.

10 b) Collection of urine samples

Prior to oral administration of drug the blank urine samples were collected from each volunteer. Urine samples of volunteer's were collected after 2, 4, 6, 8, 12 and 24 hours after drugadministration. These urine samples were stored in plastic bottles in freezer at -20?C until analysis

11 Hplc Analysis a) Preparation of mobile phase

Mobile phase was prepared by using phosphate buffer of 15 mM. the phosphate buffer was prepared by mixing of 0.288g KH2PO4 and 2.33g of K2HPO4 in the double distilled water of HPLC grade and volume was made up to 1000 ml. while for the mobile phase other reagents and chemical used are acetonitrile and methanol which are the HPLC grade. The pH of the buffer was 7.3. Mobile phase was prepared by mixing Acetonitrile, methanol and the phosphate buffer are in 30:5:65 ratio than the mobile phase was filtered in vacume filtration assembly having cellulose filter which have pore size 0.545um (Sartorius ag 37070.) than the filterd mobile phase was sonicated for the removal in any bubbles for 10 minutes. (eyela sonicator)

12 b) Chromatographic Conditions

Chromatography was performed with a high performance liquid chromatography. The HPLC system was consisted of Shimadzu SCL-10A system controller, UV visible SPD-10AV detector and LC-10AT pump with FUC-10AL VP flow controller wall. Separation was achieved at ambient temperature with Hypersil C18 BDS

250x4.6 column pore size of 5 micron. Chromatographic data was collected and analyzed using CSW32 software. And spectrophotometer (PG Instruments, model T60) was used for creatinine analysis in plasma and urine samples.

13 c) Standard preparation for blood samples

Stock solution was prepared in methanol. For preparation of standard curve of nimesulide in the plasma samples, nimesulide standard have concentration of 5, 10, 15, 25, 50, 75 and 100 ?g /ml was mixed in plasma which is drug free. This is given in table 3.2. Drug free plasma was taken firstly and then added to the stock solution of nimesulide of specific concentration. This is then centrifuge at 3500 rpm for 5 min then 50 ?l supernatant was taken into the ependorf. Then phosphate buffer having 7.3 pH was added into the supernatant. The sample was filtered by using filtrate assembly with micro syringe through 0.22 um pore size membrane filter having diameter of 0.13 mm and the 20 ?l of the such filtrate was injected into the HPLC instrument for the standard curve peak area (mv) versus plasma concentration ?g/mL of standard were ploted and a linear relationship was obtained.(Fig 3 **??**1)

14 Concentration and peak area of standard solution of Nimesulide is plasma d) Standard preparation for urine

For preparation of standard curve in urine, a stock solution of nimesulide (sigma) 1000 ug /ml = 0.01g of nimesulide and diluted up to 10 ml with double distilled methanol 1000ug/ml =1ml of 1000ug/ml. Standard solutions having different concentrations of nimesulide from this stock solution were prepared. For concentration of 100?g/mL, 1mL of stock solution (1000 ?g/mL) was diluted up to 10mL with double distilled methanol.

Nimesulide standard urine having concentration of 5, 10, 15, 25, 50, 75 and 100?g/ml of Nimesulide were prepared in drug free urine given in the table 3.3. This is then centrifuge at 3500 rpm for 5 mints. Then 50 ?l supernatant was taken into the ependorf. Then buffer having 7.3 pH which is phosphate was added into the supernatant. The sample was filtered by using filtrate assembly with microsyringe through 0.22um pore size membrane filter having diameter of 0.13 mm and the 20

15 e) Statistical Analysis

Statistical analysis was performed by expressing all the data as mean, standard error of mean. The effect of pH and diuresis on renal clearance of nimesulide is to be studied by regression analysis **??**Steel et al., 1997).

16 VII.

17 Results and Discussion

Within 24 hours of oral administration, some 50-70% of the dose on Mean was excreted in the urine as unchanged drug. Over the dose range of 0.3-30 mg/kg nimesulide, there was no dose-dependent effect on total or renal clearance, (Kerola et al., 2009). 70% of a nimesulide dose being excreted unchanged in urine with the major site of elimination which occurs by renal mechanisms. At the glomerulus nimesulide is mainly secreted and filtered by the organic cationic secretory pathway. In this way renal clearance values approximately 4 times greater than GFR **??**Dowling and Frye, 1999). The difference in the urinary excretion of nimesulide under local conditions and reported in literature is due to environmental and genetic influences on glomerular filtration rate which significantly affect the fate of drug in the body. The Mean value of the percent dose of nimesulide in urine sample was 83% +/-16%, in the earlier study was calculated by (Korsuntirat et al., 2010). The present percent dose is lower calculated as 69.30±2.18. There is difference between present study value and earlier study value due to difference in environment, temperature but major difference in the values is due to non fasting volunteers.

Studies on nimesulide suggest that it is extensively secreted from urine even though when given in small amounts. At plasma concentrations up to 30fold the tubular secretion rate of nimesulide gradually increases and higher than those values which are achieved during 100 mg/day typical oral dosing (Dowling et al., 2001).

The retention time for the present study was 6.5 min for plasma and 4.2 min for urine while according to a study it is 8.4 min **??**Dowling and Frye, 1999). The difference is probably due to storage of urine and plasma samples, environmental conditions and/or temperature. [1] [2]

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Figure 1: TB

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[Note: 10. Starek, M., and J. Krzek. 2009. Review of analytical techniques for determination ofoxicams, nimesulide and nabumetone. Drugs. 276(1): 47-52. 11.]

Figure 2:

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