Effect of uricol® and food with different samafurantin® doses on secondary pharmacokinetic parameters by applying urinary data

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Research Article

Effect of uricol® and food with different samafurantin® doses on secondary pharmacokinetic parameters by applying urinary data

Entidhar J. Al- Akkam*, Saba A. Jabir, Zainab T. Salih, Amani Shaker

ABSTRACT

Introduction: Nitrofurantoin (NFT) is abroad spectrum bactericidal antibiotic. The bioavailability of NFT is affected by many factors. Samafurantin® tablets containing 50 mg NFT were manufactured by Samarra drug industry. Urinary excretion studies were employed since; the urinary tract is the main site of NFT action and excretion. **Objective:** The objective of the study was to investigate the effect of Uricol® and food on secondary pharmacokinetic parameters of Samafurantin® tablets with different doses by applying urinary data. **Methods:** Twelve healthy male volunteers participated in this study. Urine samples were collected from each volunteer after overnight fasting at a specified time intervals which considered as a blank sample for measuring urine pH of urine. After that, volunteers were randomly divided into two groups (G1 and G2) each of six. Group 1 was administered 100 mg of NFT (Two tablets of 50 mg Samafurantin®) while, G2 was administered 200 mg of NFT (Four tablets of 50 mg Samafurantin®) as a single oral dose. Both groups administered the dose on an empty stomach (fasting), along with one Uricol® of 5 g sachet on fasting, and on full stomach after eating a standard breakfast after 1-week washout period between each experiment and another. For each experiment, urine samples were collected from each volunteer from 0.25 to 7 h post dosing. In addition, the volume of each void urine sample was measured. **Results:** Both groups (G1 and G2) showed only slight differences in the pH of urine after administration of Samafurantin® as compared with that of the blank. While, the pH of urine for both groups was higher after administration of Samafurantin® tablets along with Uricol® 5 g. In both groups, each of Uricol® and food exhibited no significant differences ($P < 0.05$) in secondary pharmacokinetic parameters of NFT; the rate constant of elimination (K_{el}) and absorption (K_a) and consequently their half-life ($t_{0.5\ el}$ and $t_{0.5\ abs}$) as long as the drug followed first-order kinetics. While significant differences ($P < 0.05$) were observed for maximum excretion rate (ExR_{max}), cumulative amount excreted in urine (CAe) and CAe as percentage of the dose. This could be attributed to the pH-change of urine by Uricol® which alkalinized the urinary and kidney tract or delaying gastric emptying by food. Same observations were attained when comparing G1 with G2 after administration of NFT on fasting. **Conclusions:** Administration of Samafurantin® tablets at higher doses, along with Uricol® or with food increases secondary pharmacokinetic parameters related to the rate and extent of absorption and elimination without significant changes in their corresponding rate constants and half-lives.

KEY WORDS: Food effect, Nitrofurantoin, Pharmacokinetics study, Secondary pharmacokinetic parameters

INTRODUCTION

Nitrofurantoin (NFT) is a semisynthetic antimicrobial drug derived from furan by addition of nitro group and a side chain containing hydantoin. Chemically, Nitrofurantoin is [1-{(5-nitro-2-furyl) methylideneamino} imidazolidine-2,4-dione]. Its empirical formula is $C_8H_6N_4O_5$. The molecular weight is 238.16 g/mol. The structural formula of NFT is shown in Figure 1.[1]

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However, it is a weak acid with pka value equal to 7, and its solubility is affected by the pH.[2]

NFT is abroad spectrum bactericidal antibiotic and has been used for prophylaxis and treatment of acute lower urinary tract infections.[3] The conventional dose of NFT is 50 mg or 100 mg 4 times daily. The bioavailability of NFT is about 90%, and it is affected by many factors such as ingestion of food, dose, particle size of the drug formulation, and pH. It appears to be more effective in acidic urine and more soluble in alkaline urine.[4]

After oral administration, NFT is well absorbed from the gastrointestinal tract with most of the absorption taking

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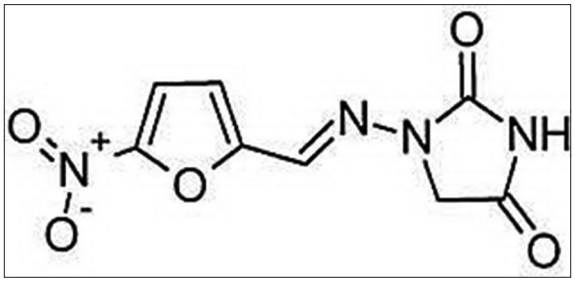

Figure 1: Chemical structure of Nitrofurantoin

place in the proximal small intestine.[5] The drug is 20–60% plasma protein bound. Nitrofurantoin is partially metabolized in the liver to form amino-nitrofurantoin. It is largely eliminated within 6–8 h. After oral administration, 30–60 % NFT is excreted intact in urine, and ~ 1 % is excreted in urine as amino-nitrofurantoin.[6]

On the other hand, Uricol®, as an effervescent granules single dose of 5 g sachets, is a multifunctional formulation composed of Hexamine (0.5 g), piperazine citrate (0.19 g), khellin (1.83 mg), and effervescent base to 5 g. Hexamine exerts antimicrobial effect against Gram-positive and Gram-negative bacteria while piperazine citrate adjusts the pH of urine and prevents urate calculi deposition. The third ingredient khellin (1.83 mg) acts as anti-spasmodic against the smooth muscle hypermotility associated with urinary tract infection. These three ingredients are completing one another so that, Uricol® is used as a urinary antiseptic, antispasmodic, and for urinary lithiasis.[7]

The objective of this study was to investigate the effect of Uricol® and food on secondary pharmacokinetic parameters of Samafurantin® tablets with different doses by applying urinary data.

Samafurantin® tablets containing 50 mg Nitrofurantoin were manufactured by Samarra drug industry (SDI). Urinary excretion studies were employed in the following investigation since; the urinary tract is the main site of NFT action and excretion.[8]

MATERIALS AND METHODS

Materials and Reagents

Nitrofurantoin 50 mg tablets (Samafurantin®, SDI, samarra, Iraq). Nitrofurantoin standard powder (Supplied from SDI., samarra, Iraq as a gift), Uricol® effervescent granules of 5 g sachets (Pharco Pharmaceuticals, Alexandrie, Egypt), buffer solutions pH 7, 4 and 10) (Weilheim, Germany), dimethyl formamide (BDH chemical Ltd. pool, England).

Study Design, Drug Administration, and Urine Sampling

Twelve healthy male volunteers participated in this study with the age between 22 and 25 years and weight in the range of 60–75 kg. They were considered healthy on the basis of medical history, physical and clinical examinations, and routine laboratory tests. Urine samples were collected from each volunteer after overnight fasting (on an empty stomach) at a specified time intervals which considered as a blank sample for measuring the pH of urine. After that, volunteers were randomly divided into two groups, each of six volunteers.

The first group (G1) was administered 100 mg of NFT (Two tablets of 50 mg Samafurantin®) while the second group (G2) was administered 200 mg of NFT (Four tablets of 50 mg Samafurantin®) as a single oral dose. Both groups administered the dose on an empty stomach (fasting state).

On an empty stomach mean, fasting overnight and drinking two glasses (500 ml) of water 2 hours before administering the tablets. After that, the required dose (either 100 mg or 200 mg of NFT) was administered with only one glass of water. Mean while, one glass of water was drinking each hour during the experiment.

After 1-week washout period, each group administered the same dose of NFT (100 mg for G1 and 200 mg for G2) along with one Uricol® of 5 g sachet also on an empty stomach (fasting). The content of the sachet was added to half a glass of water and was drinking during effervescence.

As well as, another experiment was done after another 1-week washout period. Each group administered the dose of NFT only (100 mg for G1 and 200 mg for G2) as a single oral dose after eating a standard breakfast, piece of bread and one piece of cheese (full stomach). This experiment was done by following the same program as an empty stomach (fasting).[9,10]

At each experiment 17 urine samples were collected from each volunteer according to the following time intervals; 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, and 7.0 h post-dosing. In addition, the volume of each void urine sample was measured.

pH Measurements

The degree of acidity (pH) of urine samples at each time interval was measured for blank samples and after administering NFT only as well as along with Uricol® at both doses (100 mg for G1 and 200 mg for G2) on an empty stomach. A pH-meter (Schott Gerate, Germany) was utilized. The pH measurements demonstrated the effect of Uricol® when administered along with Samafurantin® on an empty stomach.

Drug Analysis

Urine samples of each volunteer were analyzed using visible ultraviolet (UV)- Spectrophotometer (Labomed Inc., USA) at λ_{max} of NFT equal to 370 nm

which was previously determined by scanning.[1]

A calibration standard curve of NFT was constructed by plotting the absorbance against the respective concentration for a spiked urine sample with previously prepared standard solutions of NFT using a linear least squares regression analysis. The calibration standard curve was applied for the determination of NFT concentrations in the unknown urine samples.[11,12]

Data Analysis

The urinary excretion rates of NFT were calculated from the measured amount excreted in urine with a time interval. On semilog papers, the excretion rates were plotted versus midpoint time (M.P.T). The ExR_{max} was determined, and according to the standard methods, the secondary pharmacokinetics parameters of NFT including the elimination rate constant (K_{el}), absorption rate constant (K_a), elimination half-life ($t_{0.5\ el}$), and absorption half-life ($t_{0.5\ abs.}$) were calculated. As well as, the cumulative amount excreted unchanged in the urine during 7 h (cumulative amount excreted in urine($CAe^0 \xrightarrow[\text{in urine}]{7h}$) and the CAe as percentage of the dose after administration of NFT were calculated.[13]

In addition, plotting of CAe of NFT of each group versus time on ordinary paper was applied for estimation of elimination half-life ($t_{0.5\ el}$) and consequently calculation of elimination rate constant (K_{el}).[10]

Statistical Treatment of Data

Results were expressed as a ± standard deviation (SD) and percent correlation of variation (C.V. %) for each group at different time intervals.

Student's *t*-test was used to analyze the difference between two groups by utilizing SPSS18 software window. A probability value ($P < 0.05$) was considered the minimum level of statistical significance.

RESULTS AND DISCUSSIONS

Effect of Uricol® on Degree of Acidity (pH) of Urine

Minimum and maximum values of urine pH throughout the whole period of the experiment (7 h) for blank samples were found to be 6.0 and 7.35, respectively. After oral administration of NFT only, at 100 mg single dose (Two tablets of 50 mg Samafurantin®, G1), minimum and maximum values of urine pH were 6.055 and 7.147, respectively while for 200 mg dose (Four tablets of 50 mg Samafurantin®, G2), these values were 5.908 and 6.912, respectively. However, both groups (G1 and G2) showed only slight differences in the pH values compared with that of the blank. On the other hand, minimum and maximum values of urine pH were found to be 6.283 and 8.653 for G1 and 6.703 and 7.813 for G2, respectively, after administration of Samafurantin® tablets 100 mg or 200 mg along with Uricol®(5 g) so that higher urine pH values were observed for G1 and G2 after administration of Samafurantin® tablets at both doses along with Uricol®(5g). These results were illustrated in Table 1 and Figure 2.

However, pH-profile curves of these groups illustrated in Figure 2 showed that administering of Uricol®(5 g) along with Samafurantin® exhibited an obvious increase in the urine pH as compared with blank and after administration of Samafurantin® only at both doses. This effect of Uricol® was observed in G1 more than in G2. These results were due to the fact that urine is largely unbuffered and the presence of Uricol® (5 g) (alkaline drug) could counteract the acidity of urine.[14,15]

Effect of Uricol® on Secondary Pharmacokinetic Parameters of Nitrofurantoin (Samafurantin®) at Different Doses

The mean values of the secondary pharmacokinetic parameters of NFT; ExR_{max}, K_{el}, K_a, $t_{0.5\ el}$, $t_{0.5\ abs}$, and $CAe^0 \xrightarrow[\text{in urine}]{7h}$)were 6.62 mg/h, 0.305 h^{-1}, 1.0056 h^{-1}, 2.309 h, 0.694 h, and 29.598 mg,

Table 1: Effect of Coadministration of Uricol® with Samafurantin® on pH of Urine

Group (G)	Minimum pH	Maximum pH
Blank	6.0	7.35
G1 (100 mg NFT only)	6.055	7.147
G2 (200 mg NFT only)	5.908	6.912
G1 (100 mg NFT and Uricol® 5 g)	6.283	8.653
G2 (200 mg NFT and Uricol® 5 g)	6.703	7.813

Number of volunteers=12 (Blank), 6 (G1), 6 (G2)

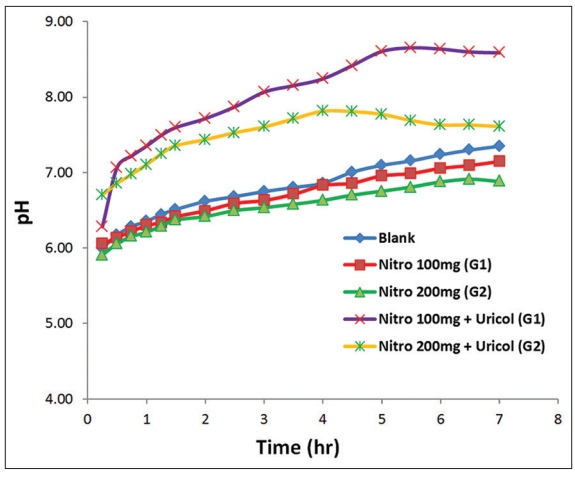

Figure 2: pH - profile of urine samples after administration of Samafurantin® at a single oral dose 100 or 200 mg only or along with Uricol® (5 g) on an empty stomach as compared with a blank

respectively. The CAe as percentage of dose was 29.598%. These results were attained for G1 after administration of NFT only at a single oral dose of 100 mg (Two tablets of 50 mg, Samafurantin®) on an empty stomach (fasting). When the same group (G1) was administered the same dose of Samafurantin® tablets along with Uricol® effervescent granules (5 g) also on an empty stomach (fasting) after 1-week washout period, these parameters were changed to 11.049 mg/h, 0.299 h^{-1}, 0.972 h^{-1}, 2.317 h, 0.716 h, and 45.327 mg, respectively. The CAe as percentage of dose was 45.327%. These results were calculated from the individual pharmacokinetic analysis of the urine concentration-time data of each volunteer as summarized in Table 2.

The pharmacokinetic parameters of NFT; K_{el}, K_a, $t_{0.5\ ele}$, and $t_{0.5\ abs}$ were calculated by plotting the excretion rate versus M.P.T on a semilog paper for each volunteer individually and according to the residual method.[16] Most volunteers represented the same time to reach maximum urinary excretion rate (ExR_{max}) which was at M.P.T of 2.75 h. Figure 3 showed the excretion rate of NFT against M.P.T. after administration of 100 mg dose only and when coadministered with Uricol® (5 g).

On the other hand, a plot of cumulative amount excreted (CAe) of NFT versus time on ordinary paper gave an approximate estimation of the elimination half-life and consequently calculation of elimination rate constant for each volunteer.[15] These results were illustrated in Table 3 and Figure 4.

As well as, the same observations on the secondary pharmacokinetic parameters of NFT were resulted for G2 volunteers after coadministration of 200 mg NFT

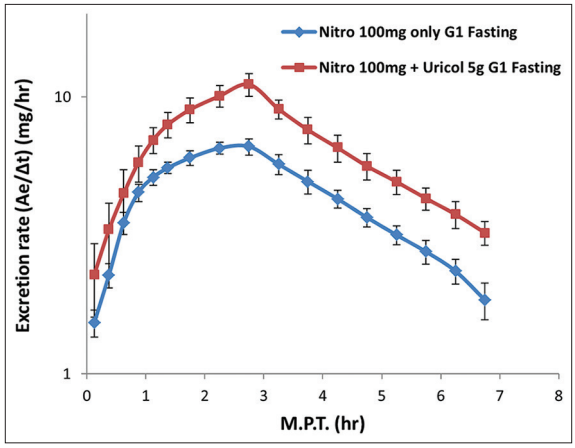

Figure 3: Effect of Uricol® (5 g) on the urinary excretion rate of Nitrofurantoin at 100 mg dose (Two tablets of 50 mg Samafurantin®) on fasting

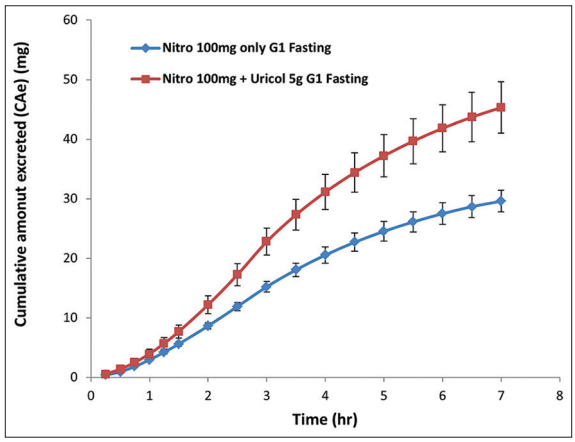

Figure 4: Effect of Uricol® (5 g) on the cumulative amount excreted in urine of Nitrofurantoin at 100 mg dose (Two tablets of 50 mg Samafurantin®) on fasting

Table 2: Effect of Uricol® (5 g) on secondary pharmacokinetic parameters of Nitrofurantoin at 100 mg dose (two tablets of 50 mg Samafurantin®) on fasting by applying urinary data

Secondary pharmacokinetic parameters	Mean ±SD, CV%	
	Nitrofurantoin 100mg only (G1)	Nitrofurantoin 100mg with Uricol® (5g) (G1)
ExR_{max} (Ae/Δt) (mg/h)	*6.62±0.444, 6.712	*11.049±1.030, 9.287
K_{el} (h^{-1})	0.305±0.04, 13.097	0.299±0.007, 2.178
K_a (h^{-1})	1.005±0.088, 8.748	0.972±0.069, 7.111
$t_{0.5\ el}$ (h)	2.309±0.325, 14.092	2.317±0.048, 2.088
$t_{0.5\ abs}$ (h)	0.694±0.06, 8.586	0.716±0.05, 7.043
$CAe^0 \xrightarrow[\text{in urine}]{7h}$ (mg)	*29.598±1.830, 6.182	*45.327±4.337, 9.568
CAe as % of dose	*29.598±1.83, 6.182	*45.327±4.337, 9.568

n=6, *Significant difference (*P*<0.05). SD: Standard devation

Table 3: The elimination half-life ($t_{0.5\ el}$) and elimination rate constant (k_{el}) resulted from a plot of cumulative amount excreted (CAe) of Nitrofurantoin versus time

Secondary pharmacokinetic parameters	Mean ±SD, CV%	
	Nitrofurantoin 100 mg only (G1)	Nitrofurantoin 100 mg with Uricol® (5 g) (G1)
K_{eL} (h^{-1})	0.283±0.006, 2.263	0.301±0.023, 7.691
$t_{0.5\ el}$ (h)	2.45±0.055, 2.236	2.317±0.183, 7.920

SD: Standard deviation

corresponding group (G1 and G2). As predicted, no significant changes in the rate constant of elimination and absorption and consequently their half-life as long as the drug followed first-order kinetics.[17–19]

On the other hand, each of the maximum urinary excretion rate (ExR_{max}), cumulative amount excreted in urine (CAe), and CAe as percentage of dose at infinite time (7 h) for both groups (G1 and G2) were significantly increased ($P < 0.05$) under the effect of Uricol® (5 g) when administered along with Samafurantin®. This could be attributed to the pH-change of urine by the presence of Uricol® (as shown in Figure 2) which alkalinized the urinary and kidney tract caused by increase in the ionization of NFT (weak acidic drug) accompanied with decreasing in the reabsorption of the unionized form through the tubular lumen of the kidney. However, drugs which alkalinize the urine increase the excretion of Nirtrofurantoin.[20,21]

Effect of Different Doses on Secondary Pharmacokinetic Parameters of Nitrofurantoin

A comparison was done between the secondary pharmacokinetic parameters of G1 and G2 after administration of Samafurantin® dose only on an empty stomach (fasting). Same observations were attained, however, no significant differences ($P < 0.05$) for; K_{el}, K_a, $t_{0.5\ el}$, $CAe^0 \xrightarrow[\text{in urine}]{} {}^{7h}$ and $t_{0.5\ abs}$ between G1 and G2 while each of ExR_{max}, and CAe as percentage of dose showed significant differences ($P < 0.05$) as illustrated in Table 5, Figures 7 and 8. These results confirmed that NFT rate processes followed first-order kinetics (dose-dependent).[19,22] These results were in agreement with the previous study reported by Watari *et al*.[23]

Effect of Food on Secondary Pharmacokinetic Parameters of Nitrofurantoin at Different Doses

After another 1-week washout period, G1 volunteers were administered 100 mg NFT (Two tablets of 50 mg Samafurantin®) as a single oral dose directly after eating a standard breakfast (full stomach). The value of ExR_{max}, K_{el}, K_a, $t_{0.5\ el}$, $t_{0.5\ abs}$, $CAe^0 \xrightarrow[\text{in urine}]{} {}^{7h}$, and CAe as percentage of dose (Four tablets of 50 mg of Samafurantin®) with Uricol® (5 g) as shown in Table 4, Figures 5 and 6.

From all the above results and by applying Student's *t*-test to analyze the differences in the pharmacokinetic parameters; K_{el}, K_a, $t_{0.5\ el}$, and $t_{0.5\ abs}$, no significant effects ($P < 0.05$) were observed for Uricol® (5 g) when administered along with Samafurantin®at 100 mg (G1) or 200 mg (G2) dose as compared with administration of Samafurantin®only for each

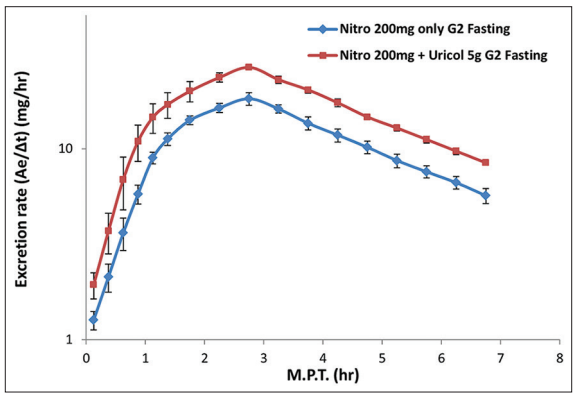

Figure 5: Effect of Uricol® (5 g) on the urinary excretion rate of Nitrofurantoin at 200 mg dose (Four tablets of 50 mg Samafurantin®) on fasting

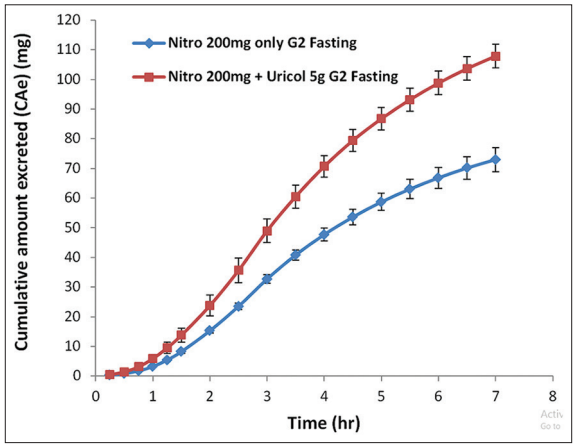

Figure 6: Effect of Uricol® (5 g) on the cumulative amount excreted in the urine of Nitrofurantoin at 200 mg dose (Four tablets of 50 mg Samafurantin®) on fasting

Table 4: Effect of Uricol® (5 g) on secondary pharmacokinetic parameters of Nitrofurantoin at 200 mg dose (four tablets of 50 mg Samafurantin®) on fasting by applying urinary data

Secondary pharmacokinetic parameters	Mean ±SD, CV%	
	Nitrofurantoin 200 mg only (G2)	Nitrofurantoin 200 mg with Uricol® (5 g) (G2)
ExR_{max} (Ae/Δt) (mg/hr)	*18.306±1.368, 7.473	*26.721±0.41, 1.533
K_{el} (h^{-1})	0.296±0.006, 1.998	0.29±0.009, 3.199
K_a (h^{-1})	0.955±0.055, 5.789	0.905±0.137, 15.152
$t_{0.5\ el}$ (h)	2.336±0.122, 5.239	2.395±0.079, 3.282
$t_{0.5\ abs}$ (h)	0.728±0.043, 5.921	0.781±0.121, 15.529
$CAe^0 \xrightarrow[\text{in urine}]{} {}^{7h}$ (mg)	*72.98±4.043, 5.54	*107.857±3.977, 3.687
CAe as % of dose	*36.49±2.021, 5.54	*53.929±1.988, 3.687

n=6, *Significant difference ($P<0.05$)

was 9.93 mg/h, 0.285h^{-1}, 0.967 h^{-1}, 2.428 h, 0.717 h, 42.35 mg, and 42.35 mg, respectively. However, no significant differences ($P < 0.05$) were observed with secondary pharmacokinetic parameters; K_{el}, K_a, $t_{0.5\ el}$, $CAe^0 \xrightarrow[\text{in urine}]{} {}^{7h}$ and $t_{0.5}$ as compared to the corresponding values on fasting state (empty stomach). On the other hand, significant increases (P <ompcompwere attained in ExR_{max}, and CAe as percentage of dose. These results were illustrated in Table 6, Figures 9 and 10.

In addition, the same observations were obtained after oral administration of 200 mg NFT for G2 as a single oral dose (4 tablets of 50 mg Samafurantin®) directly after eating a standard meal as shown in Table 7, Figures 11 and 12.

So that, for both doses (100 and 200 mg), no significant changes ($P < 0.05$) were observed by food in the rate constant of absorption and elimination since NFT follow first-order kinetics of elimination and absorption.[21] Food increased significantly the excretion rate of NFT, the CAe in urine at infinite time (7 h) and the CAe as percentage of dose in both doses which were due to the fact that the drug is a weak acid since; it became largely unionized in the stomach media at pH 1-4.[24] Furthermore, the presence of food delaying the gastric emptying, therefore, increasing the dissolution and then absorption of the unionized form of the drug through the lipid membrane of the stomach to the blood by passive diffusion, and finally increasing the urinary excretion of the drug.[25] Hence, based on the above urinary data and the significant increase ($P < 0.05$)

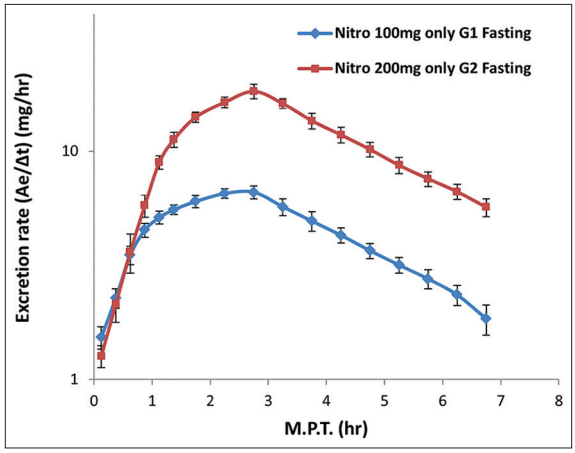

Figure 7: Effect of different doses of Samafurantin® on the urinary excretion rate

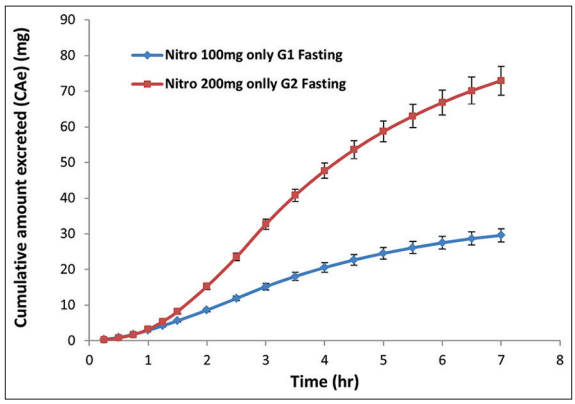

Figure 8: Effect of different doses of Samafurantin® on cumulative amount excreted in urine

Table 5: Effect of different doses on secondary pharmacokinetic parameters of Nitrofurantoin (Samafurantin®) on fasting by applying urinary data

Secondary pharmacokinetic parameters	Mean ±SD, CV%	
	Nitrofurantoin 100 mg only (G1)	Nitrofurantoin 200 mg only (G2)
ExR_{max} (Ae/Δt) (mg/hr)	*6.62±0.444, 6.712	*18.306±1.368, 7.473
K_{el} (h^{-1})	0.305±0.04, 13.097	0.296±0.006, 1.998
K_a (h^{-1})	1.005±0.088, 8.748	0.955±0.055, 5.789
$t_{0.5\ el}$ (h)	2.309±0.325, 14.092	2.336±0.122, 5.239
$t_{0.5\ abs}$ (h)	0.0.694±0.06, 8.586	0.728±0.043, 5.921
$CAe^0 \xrightarrow[\text{in urine}]{} {}^{7h}$ (mg)	*29.598±1.830, 6.182	*72.98±4.043, 5.54
CAe as % of dose	*29.598±1.830, 6.182	*36.49±2.021, 5.54

n=6, *Significant difference (P<0.05)

Table 6: Effect of food on secondary pharmacokinetic parameters of Nitrofurantoin at 100 mg dose (two tablets of 50 mg Samafurantin®) by applying urinary data

Secondary pharmacokinetic parameters	Mean ±SD, CV%	
	Nitrofurantoin 100 mg only on fasting (G1)	Nitrofurantoin 100 mg with food (G1)
ExR_{max} (Ae/Δt) (mg/hr)	*6.62±0.444, 6.712	*9.930±0.969, 9.759
K_{el} (h^{-1})	0.305±0.04, 13.097	0.285±0.003, 1.169
K_a (h^{-1})	1.005±0.088, 8.748	0.967±0.033, 3.461
$t_{0.5\ el}$ (h)	2.309±0.325, 14.092	2.428±0.029, 1.187
$t_{0.5\ abs}$ (h)	0.694±0.06, 8.586	0.717±0.024, 3.324
$CAe^0 \xrightarrow[\text{in urine}]{} {}^{7h}$ (mg)	*29.598±1.83, 6.182	*42.35±4.059, 9.584
CAe as % of dose	*29.598±1.83, 6.182	*42.35±4.059, 9.584

n=6, *Significant difference (P<0.05)

Table 7: Effect of Food on secondary pharmacokinetic parameters of Nitrofurantoin at 200 mg dose (four tablets of 50 mg Samafurantin®) by applying urinary data

Secondary pharmacokinetic parameters	Mean ±SD, CV%	
	Nitrofurantoin 200 mg only on fasting (G2)	Nitrofurantoin 200 mg with food (G2)
ExR_{max} (Ae/Δt) (mg/h)	*18.306±1.368, 7.473	*25.593±1.576, 6.157
K_{el} (h^{-1})	0.296±0.006, 1.998	0.286±0.011, 3.754
K_a (h^{-1})	0.955±0.055, 5.789	0.898±0.068, 7.555
$t_{0.5\ el}$ (h)	2.336±0.122, 5.239	2.425±0.094, 3.888
$t_{0.5\ abs}$ (h)	0.728±0.043, 5.921	0.776±0.061, 7.829
$CAe^0 \xrightarrow[\text{in urine}]{} ^{7h}$ (mg)	*72.98±4.043, 5.54	*102.796±6.01, 5.847
CAe as % of dose	*36.49±2.012, 5.54	*51.398±3.005, 5.847

n=6, *Significant difference (*P*<0.05). SD: Standard deviation

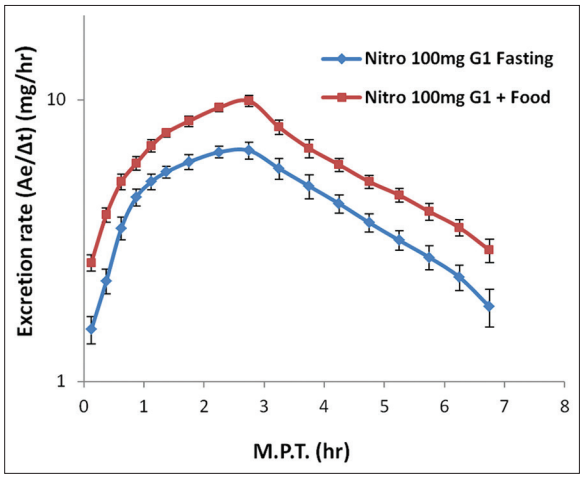

Figure 9: Effect of food on the urinary excretion rate of Samafurantin® at 100 mg dose

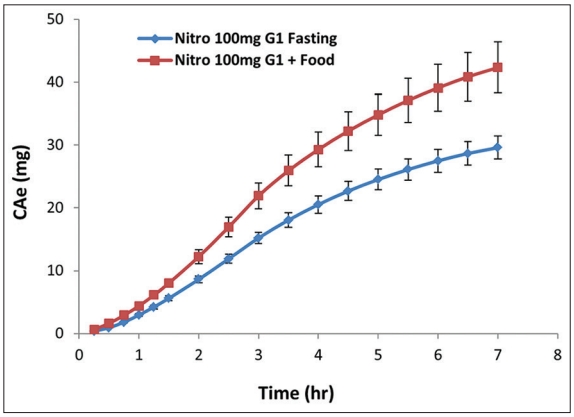

Figure 10: Effect of food on the cumulative amount excreted in the urine of Samafurantin® at 100 mg dose

in the CAe in urine, food effect involved only the extent of absorption but not the rate of absorption of the drug which was not significantly increased. These results were agreed with the study made on Nigerian (non-European) meal effect on the bioavailability of NFT in man reported by Ogunbona and Oluwatudimu.[26]

Finally, Samafurantin® tablets (100 mg or 200 mg) must be administered with food to improve its absorption (bioavailability).[27,28]

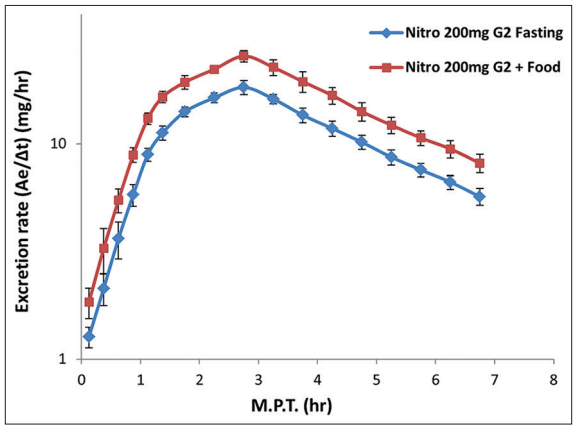

Figure 11: Effect of food on the urinary excretion rate of Samafurantin® at 200 mg dose

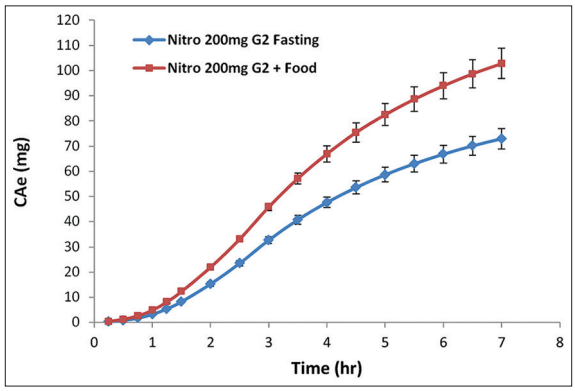

Figure 12: Effect of food on the cumulative amount excreted in the urine of Samafurantin® at 200 mg dose

CONCLUSIONS

Administration of Samafurantin® tablets at higher doses, along with Uricol® or with food increases secondary pharmacokinetic parameters related to the rate and extent of absorption and elimination without significant changes in their corresponding rate constants and half-lives. However, the patient should be advised to administered Samafurantin® with food or Uricol® to improve its absorption (bioavailability) and to increase urinary accumulation so that may exert a more antibacterial effect on the urinary tract.

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