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Original Article

Effect of Short-Term Use of Different Non-Steroidal Anti-Inflammatory Drugs on Renal Function During Fasting in Ramadan

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ABSTRACT. This study was conducted to determine the combined effect of Ramadan fasting and short-term use of different non-steroidal anti-inflammatory drugs (NSAIDs) on renal function in healthy volunteers. The study subjects were assigned to six different groups, five of whom took different NSAIDs (namely nabumetone, indomethacin, diclofenac, sulindac, tenoxicam) and the sixth was a control group. Data were collected on serum sodium, chloride, potassium, urea, creatinine, bicarbonate and uric acid as well as urinary osmolarity, sodium, potassium, chloride and urea. These measurements were taken before fasting, 10 days into fasting while using NSAIDs, and five days after stopping the use of NSAIDs. The results showed slight changes in serum and urine measurements during fasting while using NSAIDs. These changes, although were significant in some cases, were within the normal range and were noted in all the study groups including the control group. We conclude that short-term use of NSAIDs in healthy subjects during fasting is not associated with any major adverse effects on the renal function.

Key words: NSAIDs, Fasting in Ramadan, Changes in renal functions.

Introduction

Ramadan is the ninth lunar month of the muslim calendar year, when it is obligatory for all adult, healthy Muslims to observe complete fasting from dawn to sunset. Between sunset and dawn, they are allowed to eat and drink leisurely. Lack of fluid intake during the daytime may influence the fluid and electrolyte balance, and prolonged fasting may lead to hyperuricemia (1-5). Restricted water intake during fasting in Ramadan coupled with water loss especially in hot climate could result in a decrease in intravascular volume. This would activate local vasoregulatory

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mechanisms and increase prostaglandin production in the kidney which would result in improved renal blood flow (6).

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of a variety of articular and non-articular diseases. They principally act as inhibitors of prostaglandin synthesis (6). This would make their use not desirable in situations that are associated with decreased local intravascular volume. In this paper, we report the results of the short-term use of a number of NSAIDs on renal function as reflected by changes in a number of urinary and serum parameters. This was compared to the effect of fasting alone in a control group.

Materials and Methods

One hundred and fifty volunteers were recruited from the hospital staff and medical students of the College of Medicine, King Saud University, Riyadh. They did not have any history of peptic ulcer or renal disease and they all consented to participate in the study. The study subjects were randomly allocated to one of six groups, five of which were treatment groups while the sixth was a control group. Each of the five treatment groups were administered one of the NSAIDs daily, the details of which are given in Table 1. The subjects were instructed to take the NSAIDs for 10 days from the beginning of Ramadan, immediately after breaking the fast on each day.

Urine and blood samples were taken at three successive time points for each subject; the first samples (SI) were collected 1-2 days before the start of Ramadan; second samples (S2) 10 days into Ramadan corresponding to the last day of drug administration; and the third samples (S3) five days later. On each occasion, the urine and blood samples were collected 3 hours before breaking the fast. Blood samples (4 ml) were collected in plain glass vacutainer tubes and allowed to clot in a water bath at 37° C. Serum was separated by centrifugation at 3000 rpm for 5 minutes. At the same time, a urine sample was collected. Aliquots of both serum and urine were stored in a deep freezer at - 40° C until assayed at a later date.

Serum and urinary levels of urea, creatinine, sodium, potassium, chloride and bicarbonate were assayed in an automatic analyzer (Astra & Beckman). Urine osmolarity was determined by Advanced Digimatic Osmometer (Model 3DII). Uric acid was measured by American Monitor Parallel Analyzer.

Statistical Analysis

The data collected were analysed by the statistical software package SYSTAT on a microcomputer. The descriptive statistics (means and standard deviations) of each biochemical variable was computed for each treatment and control group as well as for each occasion the samples were collected. Because these biochemical measurements were made at successive time points on the same groups of subjects, random fluctuations

Table 1. The distribution of the study subjects according to the drug taken (n = 117)

Type of Drug	Dosage	No. of Subjects
1. Tenoxicam (Tilcotil)	20 mg	24
2. Nabumetone	1000 mg	23
3. Diclofenac (Voltaren-R)	100 mg	18
4. Indomethacin-SR	75 mg	17
5. Sulindac	400 mg (in 2 doses)	14
6. No Drug (control)		21

on these occasions are unlikely to be independent. But since the main interest is changes in these measurements, a univariate analysis was carried out by comparing the biochemical measurements at 10 days in Ramadan with the initial readings 1-2 days before Ramadan using the paired t-test for dependent samples. The same procedure was used to compare the measurements at 15 days with the initial readings. The tests were considered significant if they reached the 5% probability level. The effect of the drug was assessed by comparing the mean differences in the six groups using the one-way analysis of variance approach. A further multivariate analysis, the analysis of covariance, was used to compare the measurements between the six groups at the completion of the drug, 10 days into Ramadan, taking the initial measurements before Ramadan as a covariate. The exercise was also repeated for the third measurements 15 days into Ramadan, but now the earlier measurements (initial and at 10 days) were used as covariates.

Results

There were 117 volunteers who had complete records at the end of this study, thus giving an overall dropout rate of 22% with the sulindac group having the highest dropout rate of 44%. The sex distribution of the participants was 42.3% males and 57.7% females and their age ranged between 20 and 42 years. The result of a one-way analysis of variance for the comparison of the average age between the five treatment and control groups showed no statistically significant differences between them (P>0.6). Also, the sex distribution among the six groups was not statistically significant (P>0.8).

Table 2. Biochemical parameters (mean ± SD) in the serum samples

Parameters		Nabumetone	Indomethacin	Sulindac	Diclofenac	Tenoxicam	Control
Sodium	SI	139(±1.9)	140.3(±2.3)	139.4(±2.4)	139.6(±2.2)	139.9(±2.5)	140.0(±2.3)
(mmol/L)	S2	144(±5.2)	143.1(±4.8)	143.6(±2.5)	143.5(±4.4)	144.6(±4.5)	144.5(±4.0)
	S3	142(±4.2)	146.2(±2.7)	147(±3.2)	145.5(±4.0)	142(±11.3)	143.2(±3.2)
Potassium	SI	4.04(±0.23)	4.0(±0.2)	4.16(±0.31)	4.05(±0.32)	■ 3.9(±0.35)	4.0(±0.38)
(mmol/L)	S2	4.37(±0.29)	4.4(±0.8)	4.26(±0.36)	4.4(±0.67)	4.25(±0.28)	4.4(±0.57)
	S3	4.27(±0.4)	4.6(±0.4)	4.56(±0.9)	4.49(±0.4)	4.4(±0.47)	4.8(±0.62)
Chloride	SI	102.1(±2.9)	103.7(±1.7)	102.9(±2.0)	102.3(±2.2)	102.8(±2.7)	103.2(±2.8)
(mmol/L)	S2	108.5(±4.0)	105.8(±5.2)	107.6(±4.97)	107.1(±6.0)	110.3(±4.6)	108.7(±4.7)
	S3	107.1(±3.2)	108.5(±4.0)	110.5(±3.2)	109.2(±3.3)	108.7(±4.8)	107.3(±2.9)
Urea	SI	4.85(±0.86)	4.49(±1.16)	4.42(±1.2)	4.18(±0.92)	4.5(±0.8)	4.60(±1.0)
(mmol/L)	S2	5.17(±1.29)	5.29(±0.92)	5.57(±1.3)	4.83(±1.1)	5.3(±1.0)	4.65(±1.2)
	S3	5.56(±0.72)	4.9(±1.26)	5.67(±1.59)	5.41(±1.53)	5.05(±l.l)	4.84(±1.0)
Creatinine	SI	80.5(±13.5)	79.9(±21.4)	87.4(±22.1)	83.1(±21.3)	71.08(±14.1)	75.5(±19.7)
(/jmol/L)	S2	70.8(±19.5)	77.6(±13.1)	72.2(±12.2)	71.9(±18.2)	68.0(±11.2)	65.5(±20.0)
	S3	67.3(±16.6)	73.4(±13.1)	73.6(±14.2)	74.8(±31.7)	65.7(±14.3)	67.8(±16.2)
HCO3	SI	25.1(±3.6)	21.6(±2.8)	21.5(±3.2)	21.6(±3.2)	22.3(±3.0)	22.2(±3.2)'
(mmol/L)	S2	16.9(±2.0)	19.1(±2.8)	19.5(±3.7)	19.3(±2.4)	18.3(±2.7)	18.4(±3.5)
	S3	17.5(±1.6)	16.7(±2.1)	16.7(±3.5)	17.4(±3.0)	16.3(±2.0)	17.7(±2.7)
Uric Acid	SI	0.293(±0.1)	0.299(±0.1)	0.323(±0.1)	0.30(±0.1)	0.283(±0.1)	0.286(±0.1)
(/jmol/L)	S2	0.307(±0.1)	0.352(±0.1)	0.278(±0.1)	0.313(±0.1)	0.296(±0.1)	0.311(±0.1)
	S3	0.24(±0.1)	0.305(±0.1)	0.258(±0.1)	0.252(±0.1)	0.239(±0.1)	0.236(±0.1)

= Samples before Ramadan
= Samples 10 days into Ramadan corresponding to last day of drug administration.
= Samples 15 days into Ramadan.

The summary statistics showing the mean and standard deviation of each biochemical parameter for the serum and urine samples are presented in Tables 2 and 3, respectively.

Serum Samples

While the values of serum bicarbonate and creatinine decreased significantly 10 days into Ramadan (P<0.02), the values of sodium, potassium and chloride increased. Also, the decrease in serum bicarbonate was significantly lower in the nabumetone group compared to other groups (P<0.05). The decrease in the other serum values was not significantly different between the different treatment and control groups even 15 days into Ramadan (P>0.2). Ten days into Ramadan, corresponding to the time the drugs were stopped, serum uric acid levels increased slightly in all treatment and control groups except the sulindac group. However, the changes were not statistically significant (P>0.2), and 5 days later, there was a decrease below the initial values except for the indomethacin group (P>0.02).

Table 3. Biochemical parameters (mean ± SD) in the urine samples

Parameters		Nabumetone	Indomethacin	Sulindac	Diclofenac	Tenoxicam	Control
Sodium (mmol/L)	SI S2 S3	188.4(±71.0) 155(±67.0) 142.7(±44.0)	133.0(±51.7) 138.1(±53.0) 152.9(± 67.2)	187.2(±86.4) 132.5(±61.5) 154.5(±64.8)	167.1(±65.7) 131.1(±76.3) 111.9(±57.8)	165.0(±51.6) 137.0(±57.1) 162.9(±51.9)	170.4(±86.1) 130.8(±66.0) 188.8(±91.0)
Potassium (mmol/L)	SI S2 S3	94.9(±27.4) 70.3(±30.0) 56.8(±14.0)	103.2(±29.5) 71.8(±26.0) 78.4(±22.8)	97.1(±30.8) 78.4(±28.2) 75.3(±25.1)	100.7(±26.0) 67.3(±27.8) 54.5(±21.6)	119.8(±43.0) 8O.8(±36.6) 58.7(±18.2)	102.7(±31.3) 84.9(±38.9) 70.0(±19.7)
Chloride (mmol/L)	SI S2 S3	227.4(±75.4) 161.4(±53.9) 157.3(±50.3)	218.9(±76.9) 168.3(±50.4) 181.8(±77.7)	253.5(±91.4) 160.3(±69.9) 201.5(±63.4)	252.6(±88.2) 155.0(±82.1) 132.9(±70.7)	210.8(±64.9) 162.9(±64.5) 196.0(±55.7)	268.0(±94.0) 15O.8(±61.O) 202.3(±70.0)
Urea (mmol/L)	SI S2 S3	299.9(±79.5) 226.6(±62.0) 208.5(±28.0)	298.9(±81.7) 277.8(±61.7) 223.6(±52.6)	300.5(±93.9) 244.5(±55.4) 253. Kr45.4)	298.4(±98.3) 265.0(±64.8) 229.7(±50.8)	312.3(±101.3) 228.2(±44.6) 240.0(±39.7)	281.1(±55.4) 242.4(±70.3) 261.5(±110.4)
Creatinine (µmol/L)	SI S2 S3	10.8(±1.8) 11.0(±3.0) 11.3(±2.4)	10.2(±2.0) 14.9(±3.6) 12.1(±2.5)	10.6(±2.3) 13.8(±5.0) 11.3(±1.7)	10.9(±2.7) 13.1(±5.5) 11.6(±2.5)	10.4(±2.4) 11.2(±3.6) 11.8(±2.1)	11.4(±1.86) 11.4(±1.9) 12.3(±4.9)
Osmolarity (mmol/L)	SI S2 S3	646.6(± 179.2) 619.2(±160.1) 593.6(± 187.0)	751.5(± 152.2) 630.9(± 108.1) 664.7(± 121.6)	753.9(±140.8) 636.9(±80.1) 707.6(±76.0)	710.2(±114.4) 620.7(±153.5) 539.9(±206.1)	685.9(±148.3) 674.3(±142.2) 646.6(±130.5)	727.9(±128.1) 633.3(±89.6) 580.0(±206.6)
Uric Acid (µmol/L)	SI S2 S3	1.015(±0.0005) 1.019(±0.002) 1.018(±0.003)	1.019(±0.003) 1.017(±0.002) 1.019(±0.002)	1.021(±0.001) 1.018(±O.OO3) 1.018(±0.002)	1.019(±0.004) 1.018(±0.002) 1.018(±0.003	l.018(±0.004) 1.020(±0.006) 1.017(±0.003	1.020(±0.004 1.020(±0.003) 0.019(±0.005)

s1= Samples before Ramadan
s2= Samples 10 days into Ramadan corresponding to last day of drug ,
s3=administration.

Urine Samples

In the urine samples, the values of urea, 10 days into Ramadan were significantly reduced (P<0.05) in all treatment and control groups. In addition, there were significant differences in the urea levels between the six groups,'10 days, and 15 days into Ramadan, after controlling for the initial values (P<0.03). A pairwise comparison showed that the nabumetone group had significantly lower values than other groups except the tenoxicam group at each successive time points. Also, the mean creatinine was significantly different between the six groups. The subjects given indomethacin, sulindac and diclofenac had significantly higher urine creatinine than the other treatment groups 10 days into Ramadan (P<0.05). However, these differences were not statistically significant at the third reading, 15 days into Ramadan (P>0.05). A similar decrease was observed for sodium after 10 days into Ramadan in all six groups except the indomethacin group, where there was an increase. None of these changes observed were statistically significant (P>0.05). Other biochemical parameters including potassium, chloride, osmolarity and uric acid levels either decreased or increased 10 days and 15 days into Ramadan but the magnitude of the changes was not significantly different between the six groups (P>0.05). However, for potassium, the levels were constantly reduced in each treatment group (except the indomethacin group) 10 days and 15 days into Ramadan (P<0.05) when compared to pre-Ramadan values.

Discussion

Non-steroidal anti-inflammatory drugs are widely used in the treatment of different articular and non-articular diseases. They inhibit cyclooxygenase, the enzyme that transforms arachidonic acid to prostaglandins (6). This action is responsible for both the therapeutic as well as the side effects of these drugs.

In this study, the results showed increase in blood urea, sodium, potassium and chloride levels in the five treatment groups as well as the control group. However, the magnitude of these increases was within the normal range for the laboratory concerned and did not, at any point, reach pathological proportions. These changes may have resulted from a combination of lack of fluid intake in the face of NSAIDs intake, since it is known that in healthy, well hydrated individuals with normal kidneys, prostaglandins play little or no role in controlling renal function (6,7), but under certain conditions of local circulatory stress, prostaglandins become essential to the maintenance of adequate renal functions (8-10). Inhibition of prostaglandins by NSAIDs explains some of the renal side effects observed in predisposed patients by relative hypovolemic states such as congestive heart failure (11) and liver disease (12). These side effects include elevation in the level of blood urea, serum creatinine and a decrease in renal blood flow and urine volume.

Previous work on the effect of fasting on blood urea, serum creatinine and electrolytes showed an increase during the fasting period, but the levels returned to baseline values as soon as the fasting was over (5).

The data of this study also demonstrated an increase in serum uric acid levels in both the treatment as well as the control groups. This finding is one of the known sequelae of different types of fasting, and is attributed to a reduction in uric acid clearance, decreased glomerular filtration rate and alterations in renal transport of uric acid (1-3). Biochemical measurements in the urine showed decreased urea and increased creatinine with variable changes of sodium, potassium, chloride, uric

acid and osmolarity. However, the magnitude of these changes was not significant. The subjects in our study were all healthy young adults in airconditioned comfortable surroundings and were not exposed to circumstances of heat or dehydration usually encountered in outdoor Saudi Arabia. Taking this and the age of the study subjects into account the changes observed may reach significant levels when applied to elderly individuals with pre-existing renal, cardiac, or hepatic diseases. In such patients, the added insult of prostaglandin inhibition produced by NSAIDs to the stress of fasting may lead to clinically significant decrease in renal blood flow and hence, deterioration in renal function. It is important, therefore, to monitor for any evidence of deterioration in renal function when NSAIDs are prescribed for patients with pre-existing risk factors, especially during fasting. It must be pointed out that this study was performed during Ramadan in summer, but as mentioned earlier, in comfortable airconditioned surroundings. Different results may be obtained if a similar study is to be conducted during Ramadan in winter period. (Ramadan follows the lunar month calendar, not the Gregorian calendar and therefore the time period changes approximately in 30 years cycles).

It is concluded that short-term use of non-steroidal anti-inflammatory drugs in healthy subjects living in air-conditioned environment during fasting was associated with only slight changes in renal function. However, a study on healthy fasting volunteers living in hot climate, e.g., street workers, is needed.

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