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# Biochemical investigations into the effects of co-administration of ciprofloxacin and nicosan

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**The biochemical effects of Ciprofloxacin, a wide spectrum antibiotic, co-administered with Nicosan, an antisickling phytomedicine was analyzed for their possible drug interaction. Using standard methods for biochemical, haematological and antioxidant assays, our findings showed that Ciprofloxacin administration gave rise to increase in oxidative radical production, whereas Nicosan administration had no observable adverse effect. However, co-administration of both drugs was found to have no deleterious effects on body organs and erythrocytes. This suggests that the presence of Nicosan had a palliative effect on the oxidative free radicals produced as a result of the antibiotic administration.**

**Key words:** Ciprofloxacin, Nicosan, antioxidants, free radicals.

## INTRODUCTION

Ciprofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class (Nelson et al., 2007; Kawahara, 1998). It was first patented in 1983 by Bayer A.G. and subsequently approved by the United States Food and Drug Administration (FDA) in 1987. Ciprofloxacin has 12 FDA-approved human uses and other veterinary uses. It is a second-generation fluoroquinolone antibacterial agent. It acts by interfering with the DNA gyrase that causes DNA to rewind after being copied, which stops DNA and protein synthesis. Ciprofloxacin interacts with other drugs, herbal and natural supplements, and thyroid medications.

Nicosan is a herbal drug produced by Neimeth Pharmaceuticals, Nigeria, from the extracts of *Sorghum bicolour* leaf, *Pterocarpus osun* stem, *Piper guinense* seed and *Caryophylli* flower. It has been reported to block the polymerisation of hemoglobin S and might therefore reduce the number of sickle cells in the blood. This has been suggested to help to reduce the severity of the sickle cell disease (Iyamu et al., 2002). Red blood cell sickling involves the polymerisation of hemoglobin S (Desai, 2004). In this work, the drug interactions of Ciprofloxacin with Nicosan were studied. The aim of the study is to evaluate the biochemical and haematological effects of the co-administration of Ciprofloxacin and Nicosan *in vivo* using standard methods of assay for liver function, kidney function, haematological parameters and antioxidant enzymes.

## MATERIALS AND METHODS

### Chemicals and drugs

Drugs (Ciprogem® Ciprofloxacin 500 mg/Tablet, Nicosan® 350 mg/capsule) were obtained from a reputable pharmacy store in Lagos, Nigeria (Neimeth Pharmaceuticals). All chemicals used were of analytical grade, obtained from the Sigma chemical company, USA and used without further purification.

### Animals

Sprague-Dawley rats from the laboratory Animal Centre of the

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Nigerian Institute of Research (NIMR), Yaba, Lagos, Nigeria were used for the study. The animals were kept in a well-ventilated animal house at the annex of the laboratory Animal Centre of the College of Medicine, University of Lagos, and were acclimatized for 14 days before commencement of the study. They were each day fed with standard rabbit chow (Pfizer Feeds, Ibadan, Nigeria Plc.) and water *ad libitum.*

**Administration of drugs**

The rats were grouped into experimental and control groups A, B and C as follows: Groups A1, A2, A3, with 6 rats in each. They were dosed orally with different concentrations of only ciprofloxacin according to their body weight for a period of 5 days. A1 was given the under dose (7.22 mg/ml/180 g of rat), $A_2$ was given the normal dose (7.16 mg/ml/195 g of rat) and A3 was given the overdose of (14.35 mg/ml/195 g of rat) of ciprofloxacin. Groups B1 B2 B3 with 6 rats in each, were dosed orally with the manufacturer's recommended 350 mg/kg Nicosan per body weight dose and then immediately followed by a single dose of ciprofloxacin per body weight of different concentrations for a period of 5 days. B1 were given Nicosan with under dose of ciprofloxacin, B2 were given Nicosan and normal dose of ciprofloxacin, B3 were given Nicosan and overdose of ciprofloxacin. Group C with 6 rats were orally administered distilled water (1 ml/body weight) only for a period of 5 days and this set served as the control group.

**Collection of blood samples**

At the end of the 5 days of drug administration, the rats were euthanized by cervical dislocation and blood samples collected via venipuncture. For the haematological studies ethylenediaminetetraacetic acid (EDTA) bottles were used for the blood collections. For the antioxidant assay, liver function test and kidney function test heparin bottles were used for the blood collection. Standard biochemical, haematological and antioxidant evaluations were then carried out on the collected blood samples.

**Biochemical analysis**

All biochemical analysis (liver function test, kidney function test, and haematological assay) were all done according to standard protocols using the Roche/Hitachi 902 automated analyzer.

**Determination of total protein**

This was determined using biuret method (Gonall et al., 1949).

**Antioxidant assay**

The antioxidant enzymes activity was determined spectrometrically as follows.

***Determination of superoxide dismutase (SOD) activity***

Superoxide dismutase activity was determined by its ability to inhibit the auto-oxidation of epinephrine determined in absorbance at 480 nm as described by Sun and Zigma (1978). The reaction mixture (3 ml) contained 2.95 ml 0.05 M sodium carbonate buffer pH 10.2, 0.02 ml of the serum and 0.03 ml of epinephrine in 0.005 N HCl, was used to initiate the reaction. The reference cuvette 0.02 ml of water. Enzyme activity was calculated by measuring the contained 2.95 ml buffer, 0.03 ml of substrate (epinephrine) and change in absorbance at 480 nm for 5 min.

***Determination of catalase***

Serum catalase activity was determined according to previously described methods (Aksenes and Njaa, 1981) by measuring the decrease in absorbance at 240 nm due to the decomposition of $H_2O_2$ in a ultra violet (UV) recording spectrophotometer. The reaction mixture (3 ml) contained 0.1 ml of serum in phosphate buffer (50 mM, pH 7.0) and 2.9 of 30 mM $H_2O_2$ in phosphate buffer pH 7.0. An extinction coefficient for $H_2O_2$ at 240 nm of 40.0 $M^{-1}$ $cm^{-1}$ (Aebi, 1984) was used for the calculation. The specific activity of catalase was expressed as moles of $H_2O_2$ reduced per minute per mg protein.

***Reduced glutathione determination***

The reduced glutathione (GSH) content of tissue as non-protein sulphydryls was estimated according to the method described by Sedlak and Lindsay (1960). To the supernatant, 10% trichloroacetic acid (TCA) was added and centrifuged. 1.0 ml of supernatant was treated with 0.5 ml of Elman's reagent (19.8 mg of 5,5-dithiobisnitro benzoic acid (DTNB) in 100 ml of 0.1% sodium nitrate) and 3.0 ml of phosphate buffer (0.2 M, pH 8.0). The absorbance was read at 412 nm (Nair et al., 1991).

***Lipid peroxidation (MDA)***

Malondialdehyde (MDA), an index of lipid peroxidation, was determined using the method of Bluege and Aust (1978). 1.0 ml of the supernatant was added to 2 ml of (1:1:1 ratio) TCA-TBA-HCL reagent (thiobarbituric acid 0.37%, 0.24 N HCl and 15% TCA) tricarboxylic acid thiobarbituric acin-hydrochloric acid reagent boiled at 100°C for 15 min, and allowed to cool. Flocculent materials were removed by centrifugation at 3000 rpm for 10 min. The supernatant was removed and the absorbance read at 532 nm against a blank. MDA was calculated using the molar extinction coefficient for MDATBA-complex of $1.56 \times 10^5$ $M^{-1}$ $cm^{-1}$ (Torun et al., 2009).

**Haematological analysis**

All haematology analyses (White blood cells, red blood cell, hemoglobin, hemoglobin count, platelet, lymphocyte, neutrophils (%), lymphocytes (%), neutrophils absolute) were performed using standard procedures with the Sysmex automated analyzer (Model:KN-21N).

**Statistical analysis**

The statistical analysis of the data obtained were analysed using the student t-test and level of significance set at $p < 0.05$.

## RESULTS

### Liver function test

Table 1 shows a significant increase in the enzyme activities in the liver [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (T-BIL)] for groups A1, A2, A3 that

**Table 1.** Effect of the co-administration of ciprofloxacin and Nicosan on Liver function enzymes.

| Groups | AST | ALT (Alanine amino transferase) | ALP (Alkaline phosphatase) | T.Bil (Total bilirubin) |
|---|---|---|---|---|
| | Mean ± SEM | | | |
| $A_1$ | 205.37*±8.52 | 51.93*±3.19 | 204.28*±31.68 | 0.24±0.06 |
| $A_2$ | 264.87*±8.55 | 60.73*±2.03 | 224.88*±31.19 | 0.40*±0.02 |
| $A_3$ | 357.07*±61.69 | 73.067*±9.44 | 274.17*±22.10 | 1.33*±0.3 |
| $B_1$ | 233.53*±8.50 | 42.60±6.40 | 181.46±78.86 | 0.2467 ± 0.02333 |
| $B_2$ | 286.47*±12.25 | 130.40±93.95 | 144.91±38.56 | 0.2600±0.01732 |
| $B_3$ | 413.70*±66.87 | 47.73±4.18 | 78.70±24.74 | 0.24±0.00 |
| Control | 130.00±10.00 | 33.57±2.63 | 97.72±0.70 | 0.26±0.01 |

*Shows a significant difference at $p < 0.05$ for ALT, ALP and T.BIL concentration using student t-test. Group $A_1$: under dose (7.22mg/ml/180g of rat), $A_2$: normal dose (7.16 mg/ml/195 g of rat) and $A_3$: overdose of (14.35 mg/ml/195 g of rat) of ciprofloxacin. Group $B_1$: 350 mg Nicosan/kg rat dose and under dose of ciprofloxacin, $B_2$: were given Nicosan and normal dose of ciprofloxacin, $B_3$: were given Nicosan and overdose of ciprofloxacin. Group C: 1 ml distilled water

**Table 2.** Effect of the co-administration of ciprofloxacin and Nicosan on kidney function parameters.

| Groups | Creatinine | Urea |
|---|---|---|
| | Mean ± SEM | |
| $A_1$ | 182.07*±13.03 | 5.57±1.11 |
| $A_2$ | 209.33*±5.21 | 7.43*±0.52 |
| $A_3$ | 295.67*±3.73 | 9.93*±0.26 |
| $B_1$ | 69.30±4.64 | 7.26±0.51 |
| $B_2$ | 69.68±3.63 | 5.93±0.69 |
| $B_3$ | 62.09±5.16 | 5.26±0.67 |
| Control | 111.67±4.41 | 4.50±0.17 |

*Shows significant difference at $p<0.05$ for creatinine and urea using student t-test. Group $A_1$: under dose (7.22 mg/ml/180 g of rat), $A_2$: normal dose (7.16 mg/ml/195 g of rat) and $A_3$: overdose of (14.35 mg/ml/195 g of rat) of ciprofloxacin. Group $B_1$: 350 mg Nicosan/kg rat dose and under dose of ciprofloxacin, $B_2$: were given Nicosan and normal dose of ciprofloxacin, $B_3$: were given Nicosan and overdose of ciprofloxacin. Group C: 1 ml distilled water.

were given ciprofloxacin only as compared with the control that were given distilled water only. Groups B1, B2, B3 that were given ciprofloxacin and nicosan did show a significant decrease in the level of these enzyme activities as compared with the control that were given distilled water only.

## Kidney function test

Table 2 shows a significant increase in the level of the indicators of kidney function (that is, creatinine and urea) for groups A1, A2, A3 as compared with the control that were given distilled water only, and for groups B1, B2, B3 showed a significant decrease in the level of the parameters as compared with the control group given distilled water only.

## Total lipid and total protein test results

Table 3 shows a significant increase in the level of protein (total protein and albumin) and lipid profile (CHOL, TG) for groups A1, A2, A3 as compared with the control that were given distilled water only, while groups B1, B2, B3 showed a significant decrease in the level of the protein and lipid profile as compared with the controls that were given distilled water only.

## Antioxidant assay result

Table 4 shows a significant increase in the level of the antioxidant enzyme activities (SOD, GSH, catalase (CAT), MDA) in the serum for groups A1, A2, A3 and also for groups B1, B2, B3 as compared with the control that were given distilled water only.

## Haematological assay result

Table 5 shows a significant increase in the level of the haematological parameters (RBC, HB, PLT, HCT) in the blood for groups A1, A2, A3 as compared with the control that were given distilled water only and also a significant increase was also observed in these parameters for groups B1, B2, B3 as compared with the control that were given distilled water only. Table 6 shows a significant increase in the level of the other haematological (LYMP, NEUT (%), LYMP (%), NEUTABS) parameters in the blood for groups A1, A2, A3 as compared with the control that were given distilled water only while groups B1, B2, B3 showed a significant decrease in the level of these parameters as compared with the control that were given distilled water only.

## DISCUSSION

Ciprofloxacin inhibits an enzyme called DNA gyrase that

**Table 3.** Effect of the co-administration of Ciprofloxacin and Nicosan on total protein and lipid profile

| Groups | TG (Triacylglycerides) | CHOL (cholesterol) | (albumin) | TP (Total protein) |
|---|---|---|---|---|
| | mean ± SEM | | | |
| $A_1$ | 0.45 ± 0.04 | 1.56±0.32 | 19.50*±3.21 | 142.13*±7.97 |
| $A_2$ | 1.62*±0.12 | 3.35*±0.13 | 35.97±9.83 | 178.93*±1.16 |
| $A_3$ | 3.07*±0.22 | 6.47*±0.47 | 77.90*±3.97 | 240.96*±10.75 |
| $B_1$ | 1.56±0.67 | 1.90±0.30 | 31.27±4.37 | 100.80±24.48 |
| $B_2$ | 0.82±0.14 | 2.20±0.56 | 30.33±3.53 | 120.70±14.02 |
| $B_3$ | 1.74±0.68 | 2.01±0.28 | 28.27±2.09 | 67.46±12.90 |
| Control | 0.54±0.08 | 1.82±0.11 | 36.13±0.64 | 99.47±3.21 |

*Shows a significant drug interaction at $p < 0.05$ for TG, CHOL, ALB, and TP, using student t-test. Group $A_1$: under dose (7.22 mg/ml/180 g of rat), $A_2$: normal dose (7.16 mg/ml/195 g of rat) and $A_3$: overdose of (14.35 mg/ml/195 g of rat) of ciprofloxacin. Group $B_1$: 350 mg Nicosan/kg rat dose and under dose of ciprofloxacin, $B_2$: were given Nicosan and normal dose of ciprofloxacin, $B_3$: were given Nicosan and overdose of ciprofloxacin.
Group C: 1 ml distilled water.

**Table 4.** Effect of the co-administration of ciprofloxacin and Nicosan on antioxidant enzymes.

| Antioxidant enzymes | GSH µm/mg (glutathione peroxidase) | CAT µm/mg (catalase) | SOD µm/mg (superoxide dismutase) | MDA µm/mg (malonyldehyde) |
|---|---|---|---|---|
| | mean ± SEM | | | |
| $A_1$ | 1.88±0.06 | 112.10±0.1.82 | 24.34±0.43 | 0.10±0.001 |
| $A_2$ | 1.97±0.03 | 111.57±1.30 | 24.74±0.26 | 0.08±0.01 |
| $A_3$ | 2.65±0.64 | 356.03*±5.44 | 55.42*±1.17 | 0.77*±0.09 |
| $B_1$ | 1.12±0.15 | 190.37±10.39 | 40.90±1.22 | 0.07±0.005 |
| $B_2$ | 2.52±0.10 | 182.68±10.00 | 45.86±5.14 | 0.91±0.004 |
| $B_3$ | 7.97±0.77 | 239.58±4.95 | 52.42±0.61 | 0.07±0.005 |
| Control | 2.01±0.02 | 239.58±4.96 | 51.59±0.57 | 0.07±0.004 |

*Shows a significant difference at $p < 0.05$ for CAT, GSH, SOD and MDA, using student t-test. Group $A_1$: under dose (7.22 mg/ml/180 g of rat), $A_2$: normal dose (7.16 mg/ml/195 g of rat) and $A_3$: overdose of (14.35 mg/ml/195 g of rat) of ciprofloxacin. Group $B_1$: 350 mg Nicosan/kg rat dose and under dose of ciprofloxacin, $B_2$: were given Nicosan and normal dose of ciprofloxacin, $B_3$: were given Nicosan and overdose of ciprofloxacin.
Group C: 1 ml distilled water.

**Table 5.** Effect of the co-administration of ciprofloxacin and Nicosan on erythrocytes (A).

| Groups | RBC (red blood cell) ($^{\times}10^3$/µl) | Hb (hemoglobin) ($^{\times}10^3$/µl) | PLT (platelets) ($^{\times}10^3$/µl) | HCT (hemoglobin count) ($^{\times}10^3$/µl) |
|---|---|---|---|---|
| | mean ± SEM | | | |
| $A_1$ | 5.37±0.58 | 6.60± 0.89 | 26.03±1.85 | 8.27±0.51 |
| $A_2$ | 8.43*±0.46 | 9.84 *±0.47 | 35.60*±2.11 | 12.80*±0.55 |
| $A_3$ | 10.93*±0.85 | 13.17*±1.82 | 55.60*±5.97 | 25.47*±3.41 |
| $B_1$ | 4.49±0.96 | 8.60±1.57 | 639.67±305.86 | 27.03±5.56 |
| $B_2$ | 6.04±0.61 | 11.03±0.80 | 842.00±90.74 | 35.60±2.88 |
| $B_3$ | 5.67±0.15 | 10.40±0.50 | 1094.67±34.65 | 31.47±1.52 |
| Control | 4.20±0.12 | 6.35±0.55 | 27.00±0.72 | 8.03±0.12 |

*$p < 0.05$ Shows significant difference due to drug interaction. Group $A_1$: under dose (7.22 mg/ml/180 g of rat), $A_2$: normal dose (7.16 mg/ml/195 g of rat) and $A_3$: overdose of (14.35 mg/ml/195 g of rat) of ciprofloxacin. Group $B_1$: 350 mg Nicosan/kg rat dose and under dose of ciprofloxacin, $B_2$: were given Nicosan and normal dose of ciprofloxacin, $B_3$: were given Nicosan and overdose of ciprofloxacin. Group C: 1 ml distilled water.

**Table 6.** Effect of the co-administration of ciprofloxacin and Nicosan on erythrocytes (B).

| Groups | LYMP ($\times10^3/\mu l$) | NEU% ($\times10^3/\mu l$) | LYMP% ($\times10^3/\mu l$) | NEUTABS ($\times10^3/\mu l$) |
|---|---|---|---|---|
| | mean ± SEM | | | |
| A 1 | 680.00 ± 22.46 | 3.90±0.23 | 680.00±26.46 | 2.90*±0.12 |
| A2 | 1090.00*± 74.27 | 7.43*±0.91 | 1090.00*±74.27 | 3.93*±0.44 |
| A3 | 1343.33*±117.80 | 9.10*±0.32 | 1343.33*±117.80 | 7.40*±0.81 |
| B1 | 2.37±0.89 | 46.97±1.30 | 53.03±1.30 | 2.16±0.85 |
| B2 | 4.83±2.00 | 35.57±8.20 | 64.43±8.20 | 2.27±0.41 |
| B3 | 8.17±1.27 | 34.97±7.68 | 64.43±8.20 | 2.27±0.41 |
| Control | 692.80±72.56 | 3.43±0.67 | 692.80±72.56 | 1.33±0.22 |

*At $p<0.05$ shows a significant difference due to drug interaction. Group $A_1$: under dose (7.22 mg/ml/180 g of rat), $A_2$: normal dose (7.16 mg/ml/195 g of rat) and $A_3$: overdose of (14.35 mg/ml/195 g of rat) of ciprofloxacin. Group $B_1$: 350 mg Nicosan/kg rat dose and under dose of ciprofloxacin, $B_2$: were given Nicosan and normal dose of ciprofloxacin, $B_3$: were given Nicosan and overdose of ciprofloxacin. Group C: 1 ml distilled water.

is an essential component of the mechanism that passes genetic information onto daughter cells when a cell divides. Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. Over dose of ciprofloxacin can lead to acute renal toxicity and death (Fuchs et al., 1994). Nicosan on the other hand is a phytochemical used for the treatment of sickle cell disease, without any reported adverse effects at recommended doses (Iyamu et al., 2002).

Our present study has shown the effects of the antibacterial drug, ciprofloxacin on the antioxidant status *in vivo* and the counter effect noticed in co-administration with Nicosan. Antioxidant enzymes such as SOD, GSH, CAT and MDH help in scavenging free radicals released into the blood due to some oxidative stress activities (Matés et al., 1999). These antioxidant enzymes metabolizes oxidative toxic intermediate. The levels of these enzymes measured in our study were quite noteworthy. The effect of the co administration of ciprofloxacin and nicosan for the groups B1, B2, B3 (Ciprox + Nicosan) did not show any statistically significant drug interaction at $p < 0.05$ which suggest that there was no oxidative damage to the cells unlike the elevation of the antioxidant enzymes observed in group $A_3$ (ciprofloxacin only), where there was a significant drug interaction ($p < 0.05$) in the level of the catalase, GSH, MDA, SOD and total protein as compared with the control. This stability in antioxidant enzyme levels may be as a result of the presence of the antioxidant properties of some of the constituents of Nicosan that is, *Pterocarpus osun* stem and *Eugenia caryophyllus* fruit, which might have helped in neutralizing the effect ciprofloxacin including the case of the overdose of ciprofloxacin in group $B_3$.

In the kidney function test, the increased level in the values of the two marker enzymes, creatinine and urea in groups A1, A2, A3 signifies a liver disorder or damage (Rule et a., 2004) as compared with the control group C which has a normal range of values of these marker enzymes, but in groups B1, B2, B3, there was a statistical decrease in the values of creatinine and urea which does not signify any liver damage and could be due to the co-administration of nicosan with ciprofloxacin which helped in reducing the risk of kidney damage that might have occurred due to the administration of ciprofloxacin.

In the case of liver function test, the statistical increase in the level of the marker enzymes that is, AST, ALT, ALP, T.BIL in groups A1, A2, A3, signifies possible liver damage (Lee, 2009) as compared with the control group C which has a normal range of values of these marker enzymes, while a decrease in the level of the enzymes in group B1, B2, B3 signifies that the liver is in good order even with use of overdose of ciprofloxacin. This could also be due to the co-administration of nicosan and ciprofloxacin.

From the statistical increase in the values of the total lipid and total protein, TG, CHOL, albumin and TP in groups A1, A2, A3, as compared with the control group C which has a normal range of values of parameters, these could signify a high risk of heart disease or blood vessel disease. But in groups B1, B2, B3, the statistical decrease in the values of these parameters signifies a low risk of heart disease or blood vessel disease and these could also be due to the co-administration of nicosan and ciprofloxacin. In the haematological studies, the statistical increase in the level of the parameters that is, RBC, Hob, PLT, HCT, LYMP, NEU (%), LYMP (%), NEUTABS in group A1, A2, A3 signifies the presence of a blood disease as compared with the control group C which has a normal range of values of parameters, while in group B1, B2, B3 the statistically decrease in the level of these parameters signifies that the blood is in its right state.

Therefore, due to the potential toxicity effect of ciprofloxacin, the co-administration of ciprofloxacin with Nicosan may be beneficial as it has been shown in this study, to confer on the host some level of erythrocyte membrane protection against drug-induced oxidative

stress. This is probably due to the constituents of Nicosan which have antioxidant and blood-boosting activities that might have suppressed the oxidative stress and cell lysis that could arise by taking the different ciprofloxacin doses.

## Conclusion

From the results of our study, co-administration of ciprofloxacin and Nicosan did not show any adverse effects of drug-drug interactions. Therefore the use of ciprofloxacin can be made safer (or adverse effects of the antibiotic can be reduced) by the deliberate administration of nicosan.

## ABBREVIATIONS

**ALB,** Albumin; **ALP,** alkaline phosphatise; **ALT,** alanine amino transferase; **CAT,** catalase; **CHOL,** cholesterol; **CREAT,** creatinine; **GSH,** glutathione, reduced form; **GSSG,** glutathione, oxidized form; **HB,** haemoglobin; **HCT,** haemoglobin count; **LYMP,** lymphocytes; **MDA,** malonaldehyde; **NEUT,** neutrophils; **PLT,** platelet; **RBC,** red blood cell; **SOD,** superoxide dismutase; **TG,** triglyceride; **TP,** total protein; **WBC,** white blood cell.

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