

## INVESTIGATION OF THE EFFECTS OF SOME ANTIBIOTICS AND VITAMIN A ON THE POLYMORPHONUCLEAR LEUKOCYTE FUNCTIONS OF NEUTROPENIC CHILDREN

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### Abstract

*In this study the in vitro effects of imipenem, cefodizime, vancomycin, teicoplanin, imipenem-amikacin, imipenem-teicoplanin combinations and vitamin A at therapeutic concentration on phagocytic and intracellular killing activity of polymorphonuclear leukocytes (PMNs) in neutropenic children with acute leukemia were investigated. Twenty-one neutropenic children with mean age 7 were included in this study and were clinically divided in 3 groups. The first group included 7 nonfebrile neutropenic children not receiving chemotherapy; the second group included 7 febrile neutropenic children receiving chemotherapy; the third group included 7 nonfebrile neutropenic children receiving chemotherapy. PMNs were isolated by Ficoll-Hypaque gradient centrifugation method. C. albicans ATCC 10231 was used to measure the phagocytosis and intracellular killing activity of PMNs. Consequently, in the 1<sup>st</sup> group; the antibiotics used in our investigation and vitamin A significantly increased PMN's phagocytic activity, cefodizime showed immunomodulatory effect on the both PMN functions in the 1<sup>st</sup> and 2<sup>nd</sup> group. Additionally, vancomycin had immunomodulatory effect on the both PMN functions in the 1<sup>st</sup> group and only on the phagocytic activity in 3<sup>rd</sup> group.*

**Key words:** Polymorphonuclear leukocyte, phagocytosis, intracellular killing, neutropenia, antibiotic, vitamin A.

### Nötropenik Çocukların Polimorf Nüveli Lökosit Fonksiyonları Üzerine Bazı Antibiyotiklerin ve A Vitamininin Etkisinin Araştırılması

*Bu çalışmada terapötik konsantrasyonlardaki imipenem, sefodizim, vankomisin, teikoplanin ile imipenem-amikasin, imipenem-teikoplanin kombinasyonlarının ve A vitamininin akut lösemili nötropenik çocuk hastalarda, polimorf nüveli lökositlerin (PNL) fagositik ve hücre içi öldürme aktivitesi üzerine etkisi in vitro olarak araştırılmıştır. Yaş ortalaması 7 olan 21 nötropenik çocuk hasta, klinik olarak 3 gruba ayrılarak çalışmaya dahil edilmiştir. Birinci grupta kemoterapi almayan nonfebril nötropenik 7 çocuk, ikinci grupta kemoterapi alan febril nötropenik 7 çocuk ve üçüncü grupta kemoterapi alan nonfebril nötropenik 7 çocuk yer almıştır. PNL'ler Ficoll-Hypaque gradient santrifüjleme yöntemi ile izole edilmiştir. Fagositoz ve hücre içi öldürme aktivitesinin tayininde C. albicans ATCC 10231 suşu kullanılmıştır.*

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*Sonuç olarak, çalışmamızda kullanılan antibiyotikler ve A vitamini 1. grupta PNL'lerin fagositik aktivitesini artırmıştır. Sefodizim 1. ve 2. grupta her iki PNL fonksiyonu üzerine immünomodülatör etki göstermiştir. Buna ilaveten vankomisin 1. grupta her iki PNL fonksiyonu ve 3. grupta fagositik aktivite üzerine immünomodülatör etki göstermiştir.*

**Anahtar Kelimeler:** Polimorf nüveli lökosit, fagositoz, hücre içi öldürme, nötropeni, antibiyotik, vitamin A

## INTRODUCTION

The potential immunomodulatory effects of antibiotics on phagocytic cell functions have been demonstrated by many investigators (1). Immunomodulation by antibiotics can be beneficial especially in the treatment of infectious diseases in immunosuppressed patients (2).

Recently, especially with the use of chemotherapy in the treatment of patients with cancer the number of immunosuppressed patients has increased. Neutropenia is the most adverse effect of these drugs. Since cytotoxic drugs decrease the functions and number of neutrophils which have important roles in the defence of host against microorganisms, the risk of infection increases (3,4). This statement is particularly seen in patients with acute leukemia. The inflammatory response decreases in neutropenic patients and that is why fever is the most important symptom of infection. Wide spectrum antibiotic therapy must be immediately started in neutropenic patient with fever. In this circumstance the use of immunomodulatory antibiotics may be beneficial in the treatment of these patients (5).

The role of nutrition in the maintenance of the immune system is important. It was shown that vitamin A is necessary for the immune system and impairment of phagocytic cells and other immune system functions were documented in the absence of this vitamin (6,7,8).

The aim of our study was to investigate the effect of chemotherapy, vitamin A and some antibiotics on PMN functions which can be used in the treatment of infections in neutropenic patients. That is why the in vitro effects of imipenem, cefodizime, vancomycin, teicoplanin, imipenem-amikacin and imipenem-teicoplanin combinations and vitamin A at therapeutic concentration (safely achievable concentrations in serum) on phagocytic and intracellular killing activity of polymorphonuclear leukocytes (PMNs) in neutropenic children with acute leukemia were investigated.

## EXPERIMENTAL

### *Subjects*

Twenty-one neutropenic children with acute leukemia (6 acute myeloid leukemia, 15 acute lymphoblastic leukemia whose mean age was 7) who were treated in Department of First Pediatric Clinic, Şişli Etfal Hospital- İstanbul, were included in the study and were clinically divided into 3 groups. The 1<sup>st</sup> group included 7 nonfebrile neutropenic children who did not receive chemotherapy; the 2<sup>nd</sup> group included 7 febrile neutropenic children with fever and received chemotherapy (cytosine arabinoside + 6-mercaptopurine); the 3<sup>rd</sup> group included 7 nonfebrile neutropenic children who receive chemotherapy (cytosine arabinoside + vincristine + daunorubicin).

Blood samples were taken from 21 neutropenic children with acute leukemia who were hospitalized in the first pediatric clinic, Şişli Etfal Hospital. The patients whose neutrophil counts were under 1000/mm<sup>3</sup> were classified as neutropenic patients and those whose body temperature was more than 38.3°C were classified as patients with fever.

### *Antibiotics and Vitamin A*

The drugs used in our investigations were imipenem (50 µg/ml) (provided by Merck Sharp&Dohme Pharmaceutical Inc.), cefodizime (10 µg/ml) (provided by Aventis Farma Pharmaceutical Inc.), vancomycin (20 µg/ml) (provided by Lilly Pharmaceutical Inc.), teicoplanin (10 µg/ml) (provided by Aventis Farma Pharmaceutical Inc.), amikacin (provided by Eczacıbaşı Pharmaceutical Inc.), imipenem-amikacin combination (100+42 µg/ml), imipenem-teicoplanin combination (100+20 µg/ml) and vitamin A (0.35 µg/ml) (provided by Roche Pharmaceutical Inc.) at therapeutic concentrations. Antibiotics and vitamin A were prepared as stock solutions (ten times more than their therapeutic concentrations) in sterile distilled water (imipenem, cefodizim, teicoplanin, amikacin, vitamin A) and dimethylsulfoxide (vancomycin) and stored under -20°C in deep freeze. The stock solutions were diluted in HBSS to be 1/10 before usage.

### *Phagocytic and Intracellular Killing Activity*

Periferal blood samples (10 ml) from neutropenic children with acute leukemia were drawn with ethylenediaminetetraaceticacid (EDTA). PMNs from venous blood with EDTA ( $1 \times 10^7$  cell/ml) were isolated by Ficoll-Hypaque gradient centrifugation method which was previously described (9). Viability of PMNs was assessed by trypan blue (Sigma, 0.5% in PBS) exclusion method by counting the stained (dead) versus unstained (alive) cells on a hemocytometer. Both purity and viability were consistently greather than 99% by this method. PMNs were suspended in Hank's Buffered Salt Solution (HBSS) and cell density was adjusted by dilution ( $1 \times 10^7$  cell/ml). *Candida albicans* ATCC 10231 was used in order to measure the uptake of microorganisms by PMNs. The viability of *C. albicans* was evaluated as greather than 99% by methylene blue exclusion. Yeast cells were counted and suspended in HBSS. The suspension of PMNs in HBSS, with the different concentrations of antimicrobial agents and vitamin A, were incubated at 37°C for 30 minutes in a shaker incubator. The suspension of *C. albicans* into which a pool of human serum was added at a proportion of 4:1, was incubated in a separate tube at 37°C for 30 minutes in order to opsonize. At the end of preincubation, opsonized yeast cells ( $1 \times 10^7$  cfu/ml) incubated together with HBSS and drug PMNs ( $1 \times 10^7$  cells/ml) were combined at a proportion of 1/2 and then incubated at 37°C for 30 minutes in a shaker incubator. The final mixture contained  $5 \times 10^6$  PMNs/ml and  $5 \times 10^6$  yeast/ml. Dead yeast cells were determined by adding 1ml of methylene blue (0.01%, Sigma) at the last 5 minutes of the incubation. The phagocytic activity of PMNs was determined by counting PMNs that included phagocytosed alive and dead yeast cells and the intracellular killing activity of PMNs was determined by counting PMNs that included killed yeast cells on a slide under a microscope and the results were expressed as a percentage (10,11). All assays were performed in triplicate.

### *Statistics*

The results were expressed as means  $\pm$ SD. Statistical analyses were performed using repeated measures of ANOVA and Students Newman Keuls multiple comparisons test. P values less than or equal to 0.05 were considered to be statistically significant.

## RESULTS

PMNs' viability was assayed as 99%. *C. albicans* viability was assayed as greater than 99%. There was no statistically significant difference between the control (drug-free) values, PMN's phagocytic and intracellular killing activities of the three groups.

When compared with the control (drug-free), cefodizime and vancomycin significantly increased the phagocytic and intracellular killing activity ( $p < 0.01$ ,  $p < 0.05$  respectively) of the 1<sup>st</sup> group. While imipenem ( $p < 0.05$ ), teicoplanin ( $p < 0.01$ ), vitamin A ( $p < 0.01$ ) and imipenem-amikacin ( $p < 0.05$ ), imipenem-teicoplanin ( $p < 0.01$ ) combinations significantly increased only the phagocytic activity of this group, they did not effect the intracellular killing activity when compared with the control (drug-free) ( $p > 0.05$ ) (Table, Figure 1).

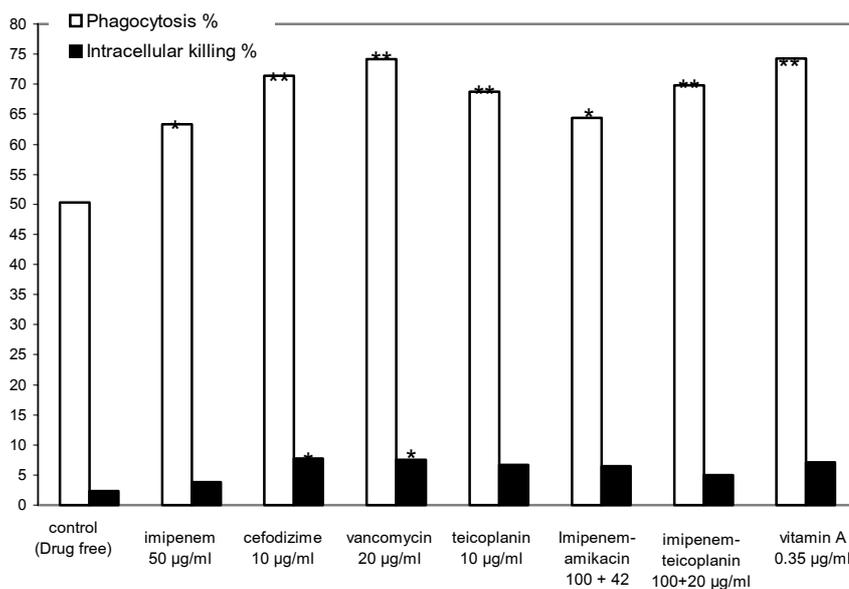
While cefodizime when compared with the control (drug-free) significantly increased the phagocytic and intracellular killing activity of the 2<sup>nd</sup> group the control (drug-free) ( $p < 0.001$ ,  $p < 0.05$  respectively), imipenem-teicoplanin combination and vitamin A significantly increased only the phagocytic activity of this group ( $p < 0.05$ ). Vancomycin also significantly increased the PMN's phagocytic activity of the 2<sup>nd</sup> and 3<sup>rd</sup> group ( $p < 0.05$ ). The other antibiotics did not significantly effect any of the PMN functions of the 2<sup>nd</sup> and 3<sup>rd</sup> group ( $p > 0.05$ ) (Table, Figure 2,3).

**Table:** The in vitro effects of vitamin A and some antibiotics on polymorphonuclear leukocyte functions (phagocytosis and intracellular killing activity) of nonfebrile neutropenic patients (n=7) and febrile neutropenic patients who received chemotherapy (n=7) and nonfebrile neutropenic patients who did not receive chemotherapy (n=7).

PMN + Drug	Nonfebrile neutropenic children not receiving chemotherapy		Febrile neutropenic children receiving chemotherapy		Nonfebrile neutropenic children receiving chemotherapy	
	%P <sup>a</sup>	%IKA <sup>b</sup>	%P	%IKA	%P	%IKA
Control (drug free)	50.29±9.55	2.29±2.98	56.29±9.62	6.43±2.37	59.29±6.24	8.00±1.53
Imipenem 50 µg/ml	63.29±4.07*	3.86±1.07	64.00±9.68	7.57±2.15	67.71±6.52	9.57±3.82
Cefodizime 10 µg/ml	71.43±10.64**	7.71±4.61*	70.86±7.96***	12.43±4.50*	69.29±10.16	7.71±2.63
Vancomycin 20 µg/ml	74.14±8.38**	7.57±3.60*	67.57±13.39*	10.14±4.78	71.29±7.87*	7.86±2.27
Teicoplanin 10 µg/ml	68.71±12.00**	6.71±5.99	60.71±9.39	7.71±2.05	62.57±4.58	7.00±1.30
Imipenem-Amikacin 100 + 42 µg/ml	64.43±9.05*	6.43±3.31	63.57±8.14	9.43±3.36	69.71±6.02	9.86±1.76
Imipenem-Teicoplanin 100+20 µg/ml	69.86±13.28**	5.00±4.04	65.71±8.92*	10.71±5.59	65.43±8.52	7.71±2.51
Vitamin A 0.35 µg/ml	74.29±13.23**	7.14±4.67	65.29±10.05*	10.29±2.75	64.57±5.71	8.43±1.90

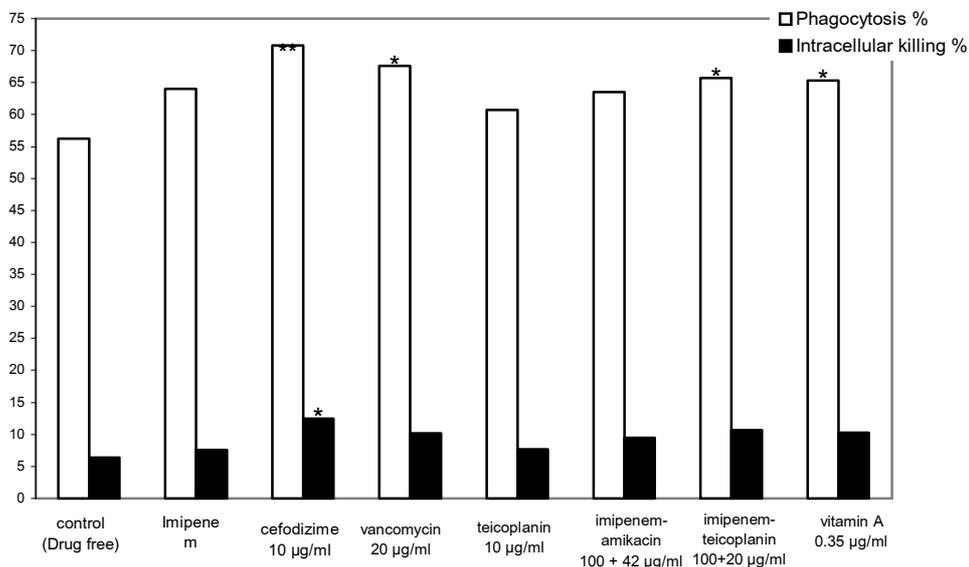
<sup>a</sup>P: Phagocytosis, <sup>b</sup>IKA: Intracellular killing activity

The results were expressed as means ±SD. Statistical analysis were performed using repeated measurements of ANOVA and Students Newman Keuls multiple comparisons test, \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  (values compared with their controls)



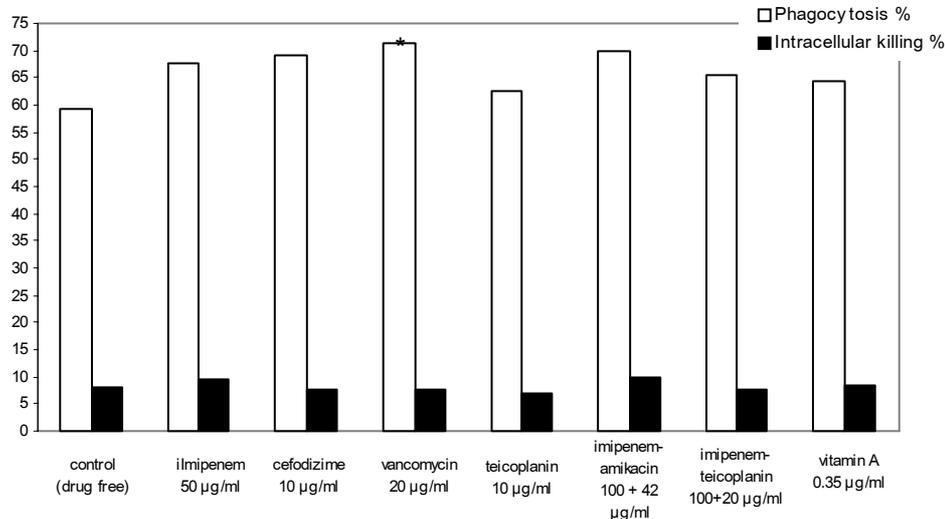
The results were expressed as means ±SD. Statistical analysis were performed using repeated measurements of ANOVA and Students Newman Keuls multiple comparisons test, \*p<0.05, \*\*p<0.01, \*\*\*p<0.001 (values compared with their controls)

**Figure 1:** The in vitro effect of vitamin A and some antibiotics on PMNs functions in nonfebrile neutropenic children who didnot receive chemotherapy (1<sup>st</sup> group).



The results were expressed as means ±SD. Statistical analysis were performed using repeated measurements of ANOVA and Students Newman Keuls multiple comparisons test, \*p<0.05, \*\*p<0.001 (values compared with their controls)

**Figure 2:** The in vitro effect of vitamin A and some antibiotics on PMNs functions in febrile neutropenic children who received chemotherapy (2<sup>nd</sup> group).



The results were expressed as means  $\pm$ SD. Statistical analysis were performed using repeated measurements of ANOVA and Students Newman Keuls multiple comparisons test, \* $p < 0.05$  (values compared with their controls)

**Figure 3:** The in vitro effect of vitamin A and some antibiotics on PMNs functions in nonfebrile neutropenic children receiving chemotherapy (3<sup>rd</sup> group).

## DISCUSSION

Recently, antibiotics which are accepted as biological response modifiers can have stimulatory effects on the immune system and may emerge as an interesting aspect of the therapy of immunocompromised patients (1,2).

Although there is an increase in the therapy success of the chemotherapy protocol for the hematopoietic malignancies, which make up most of the childhood cancers, where neutropenia is often seen and the immune system of these patients is seriously depressed, so this increases risk of infection. The only symptom of infection in neutropenic patients is fever. When there is fever ampicillin therapy must be started urgently (5). Immunomodulatory antibiotics used in the therapy of these patients and vitamin supplementation, which are used in order to support the immune system can increase the success of the therapy. Otherwise if the antibiotics have negative effects on the immune system they can negatively affect the therapy of immunosuppressed patients or extend the period of therapy.

The corticosteroids and cytotoxic agents used in the therapy of patients with cancer have immunosuppressive effect. Some of these drugs have been suggested to have a depressant activity on phagocytic activity, which may be detrimental, especially in patients with impaired immunity. Some studies reported that cytosine arabinoside, vincristin, daunorubicin, daunorubicin + cytosine arabinoside combination decrease PMN's phagocytic activity but vincristine dose not affect PMN's intracellular killing activity (3,4,12).

In our study the 2<sup>nd</sup> and 3<sup>rd</sup> groups were given cytosine arabinoside + 6-mercaptopurine and cytosine arabinoside + vincristine + daunorubicin respectively. The drugs used in the chemotherapy or the illness can be the cause of the differences of the effect of the drugs

between the three groups. The stimulatory effect of fever or possible infection can be the cause of stimulatory effect of more drugs on the 2<sup>nd</sup> group than the 3<sup>rd</sup> group.

Studies carried out with imipenem, which was shown to be successfully used in the therapy of febrile neutropenic patients, demonstrated that this antibiotic significantly increased the PMN's phagocytic and intracellular killing activity at sub-MIC concentrations in healthy subjects (13), and did not affect the PMN's phagocytic and intracellular killing activity of chronic hepatitis B patients at 30 µg/ml (14).

Imipenem-amikacin combination, which has synergistic effect on the therapy of febrile neutropenic patients is also used (15).

The result of studies carried out with imipenem are different since the 1<sup>st</sup> group in our study did not receive chemotherapy so this can be the reason for the increase of phagocytic activity with imipenem and imipenem-amikacin combination. However the intracellular killing activity of the 1<sup>st</sup> group and both PMN functions of the 2<sup>nd</sup> and the 3<sup>rd</sup> groups did not significantly increase.

Recently, there was an increase in gram positive bacterial infections in patients with cancer, so vancomycin and teicoplanin addition was suggested for empiric therapy (16).

Studies carried out with vancomycin (50-100 mg/L) and teicoplanin at therapeutic doses increased the phagocytosis of neutrophils against *S. aureus* (17), vancomycin (6-25 mg/L) and teicoplanin at therapeutic doses did not affect the phagocytosis of PMNs against *C. albicans* in healthy subjects (18). Vancomycin and teicoplanin at therapeutic concentrations did not effect the Balb/c mice PMN's phagocytic activity (19), teicoplanin (12 mg/kg) used in the prophylaxis of patients with cardiopulmonary bypass and teicoplanin used in the therapy of patients with burns did not affect the PMN's intracellular killing activity (20), teicoplanin used at therapeutic concentrations did not effect the phagocytic activity of human PMN's but it increased the PMN's intracellular killing activity of healthy subjects and patients with chronic granulomatosis (21). In our study imipenem-teicoplanin combination significantly increased PMN's phagocytic activity of the 1<sup>st</sup> and 2<sup>nd</sup> groups (respectively  $p < 0.01$ ,  $p < 0.05$ ). It also increased the phagocytic activity in the 3<sup>rd</sup> group, but this was not statistically significant.

In our study vancomycin at concentration 20 µg/ml significantly increased the PMN's phagocytic activity in all groups and significantly increased the PMN's intracellular killing activity in the 1<sup>st</sup> group. The results of our study are different from the literature because of the properties of our patients.

Cefodizime restored the immune parameters when the phagocytic function are impaired (1), it also increased the PMN's phagocytic and intracellular killing activity of patients with severe bacterial infections (22), patients with chronic hepatitis B, patients with chronic renal failure (23), patients with mutiple myeloma (24) and healthy volunteers (25).

The results of different studies showed that cefodizime significantly increased the PMN functions of patients with different illnesses and healthy volunteers. In our study cefodizime significantly increased both PMN functions of the 1<sup>st</sup> and 2<sup>nd</sup> groups. It also increased the PMN's phagocytic activity in the 3<sup>rd</sup> group, but this was not statistically significant. Cefodizime increased the PMN's phagocytic activity of the 2<sup>nd</sup> group much more statistically significant than the 1<sup>st</sup> and 3<sup>rd</sup> group and this might be because of the stimulatory effect of the fever and at the same time the immunomodulatory effect of cefodizime.

Many authors have pointed out a relationship between fever and immunity. Pramanik et al. (26) demonstrated febril responses up to 40°C have been shown to play a beneficial role in the PMN functions. They concluded that the phagocytic index of healthy young volunteers significantly increased at 38°C and 39°C when compared with that of at 37°C but it did not significantly increase when incubated at 40°C. Gomez et al. (27) showed that the phagocytic index of young adults significantly increased at 39°C and 41°C.

Vitamin A is a vital vitamin for the maintenance of the immunity. Vitamin A increases the immunity against infections in animals and particularly children (8). It was shown that PMN's phagocytic activity and oxidative molecule amount decreased in mice which were vitamin A deficient (6,7). It was also shown that vitamin A (195.000 IU/day/orally) increased PMN's phagocytic and intracellular killing activity in patient with measles when used for 2 days (28).

These studies have shown that vitamin A can have immunomodulatory effects on PMN functions. In our study vitamin A (0.35 µg/ml) significantly increased PMN's phagocytic activity in the 1<sup>st</sup> and 2<sup>nd</sup> group (p<0.01, p<0.05 respectively). It also increased the phagocytic activity in the 3<sup>rd</sup> group, but this was not statistically significant.

In the immunocompromised patients this enhancement of phagocytic activity may be clinically significant.

## CONCLUSION

Consequently, in our study all of the antibiotics used which are used in the therapy of neutropenic children have especially immunomodulatory effects on the PMN functions of neutropenic patients who did not take chemotherapy. Cefodizime showed immunomodulatory effect by increasing both PMN functions in febrile patients who were receiving chemotherapy and also in nonfebrile patients who were not receiving chemotherapy. It is conceivable that a drug with a immunomodulatory effect on PMN functions would be beneficial in the defence against infections seen cancer.

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