INFLUENCE OF FORTY-TWO ANTIMICROBIAL AGENTS ON THE CHEMILUMINESCENCE RESPONSE OF HUMAN PHAGOCYTIC CELLS

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Chemiluminescence (CL) is a sensitive indicator of phagocytosis and intracellular killing. The effect of forty-two antimicrobial agents on the luminol-enhanced CL of polymorphonuclear leukocytes (PMN) or whole blood was studied. After 10 min preincubation of cells with each drug at various concentrations, the CL response of phagocytic cells stimulated with non-opsonized zymosan or phorbol myristate acetate (PMA) was measured for 20 min. At therapeutic concentrations, sulfamethoxazole (SMX) and trimethoprim (TMP) showed significant CL suppression. Minocycline (MINO) and doxycycline (DOXY) also reduced CL at rather high concentrations (more than 12.5 μg/ml). However, twenty-seven β-lactam antibiotics, four aminoglycosides, erythromycin, clindamycin, fosfomycin, vancomycin and three antifungal agents did not inhibit CL at therapeutic concentrations. None of the antimicrobial agents enhanced the CL response from phagocytic cells in our study.

These results suggest that MINO, DOXY, SMX and TMP clinically cause a reduction in the antimicrobicidal activity of phagocytic cells. Especially in the treatment of immunocompromised patients with already-impaired antimicrobicidal activity, those drugs that inhibit the CL response *in vitro* may further reduce or suppress the function of phagocytic cells. However, the clinical significance of these observations remains to be determined.

Key words : Phagocytic cells, Chemiluminescence, Antimicrobial agents

INTRODUCTION

A functioning host defense mechanism is necessary for effective antimicrobial chemotherapy. Polymorphonuclear leukocytes (PMN) serve as the first line of host defense against invading bacteria. Recently, several antimicrobial agents have been reported to influence the function of phagocytic cells[1,2]. Some agents directly enhance chemotaxis, phagocytosis and the antimicrobicidal activity of PMN[3], or indirectly enhance the function of phagocytic cells (uptake or killing of bacteria) by inducing chemical or morphological changes in microorganisms at subinhibitory concentrations of antibiotics[4,5]. On the other hand, some agents have been reported to inhibit human PMN function. For example, tetracyclines (TCs), aminoglycosides (AGs), trimethoprim-sulfamethoxazole (TMP-SMX), chloramphenicol (CP) and amphotericin (AMPH) reduce some PMN functions[1,6~8]. The possibility that antimicrobial agents may impair PMN functions is of particular interest since these drugs are frequently administered to immunocompromised patients. However the data published on this subject are sometimes in conflict because each investigator has used different methods to measure phagocytic cell function making the evaluation of the effects of certain antibiotics on these cells difficult. The purpose of this study was to examine whether some antimicrobial agents influence the production of oxygen-free radicals from phagocytic cells *in vitro* by measuring luminol-enhanced chemiluminescence (CL).

MATERIALS AND METHODS

Antimicrobial agents. The following antimicrobial agents were dissolved with 0.9% saline or dimethylsulfoxide (DMSO) saline and adjusted to final concentrations from 8 μg/ml to 2,000 μg/ml : benzylpenicillin (PCG), ampicillin (ABPC), cloxacillin (MCIPC), piperacillin (PIPC), aspoxicillin (ASPC), cefazolin (CEZ), cefamandole (CMD), cefotiam (CTM), cefmetazole (CMZ), cefotetan (CTT), cefbuperazone (CBPZ), cefotaxime

(CTX), ceftizoxime (CZX), cefmenoxime (CMX), cefpiramide (CPM), ceftazidime (CAZ), ceftriaxone (CTRX), cefoperazone (CPZ), cefpimizole (CPIZ), latamoxef (LMOX), flomoxef (FMOX), cefuzonam (CZON), cefminox (CMNX), cefodizime (CDZM), aztreonam (AZT), carumonam (CRMN), imipenem (IPM), gentamicin (GM), tobramicin (TOB), amikacin (AMK), habekacin (HBK), erythromycin (EM), clindamycin (CLDM), fosfomycin (FOM) vancomycin (VCM), minocycline (MINO), doxycycline (DOXY), sulfamethoxazole (SMX), trimethoprim (TMP), amphotericin (AMPH), miconazole (MCZ) and 5-fluorocytosine (5-FC).

Isolation of PMN. Freshly drawn heparinized blood (10 u/ml) from healthy human donors was collected in a sterile plastic tube, and was sedimented with 4.5% Dextran solution for 40 min and then the leukocyte-rich plasma was centrifuged at 400 G across a Ficoll-Paque gradient for 30 min. Remaining pellets in the sediment were treated sequentially with hypotonic (0.2%) and hypertonic (1.6%) saline to lyse erythrocytes. Cells were washed twice with MEM (Dulbecco modified mini-

Table 1. Effect of β-lactam antibiotics on whole blood CL stimulated with zymosan or PMA

	Zymosan induced CL				PMA induced CL		
	concentrations (μg/ml)				concentrations (μg/ml)		
Drug	1.6	50	100	200	1.6	50	100
PCG	104±3	108±5	109±7	110±6	102±4	108±6	112±8
ABPC	96±2	92±6	95±5	95±7	105±3	106±4	102±4
MCIPC	98±3	95±7	103±7	98±6	98±4	106±7	110±2
PIPC	99±8	97±2	96±4	94±8	102±7	92±3	95±5
ASPC	104±6	92±3	94±4	98±4	99±6	103±3	102±3
CEZ	101±3	98±2	96±4	98±3	106±2	96±8	93±7
CMD	100±5	101±3	102±6	102±4	98±4	102±3	108±4
CTM	102±3	98±6	105±2	106±3	92±8	96±3	104±2
CMZ	107±2	97±3	109±4	104±4	102±4	99±6	102±3
CTT	100±6	106±4	102±6	100±3	101±6	96±7	100±7
CBPZ	104±3	104±3	108±6	102±4	96±7	100±3	104±6
CTX	109±6	101±6	97±6	99±5	97±7	105±3	101±6
CZX	101±3	98±3	96±3	99±4	97±6	96±6	102±5
CMX	108±5	102±8	99±5	103±3	99±5	92±7	107±9
CPM	102±6	105±8	104±7	102±4	96±7	97±9	102±10
CAZ	108±4	103±2	97±4	99±5	109±6	100±2	104±2
CTRX	106±3	104±3	112±8	110±7	104±3	95±6	103±4
CPZ	97±3	90±3	89±8	92±8	104±8	108±18	103±7
CPIZ	109±6	109±3	114±5	114±7	116±8	102±8	105±4
LMOX	102±3	101±4	97±5	99±5	103±4	99±2	98±4
FMOX	108±6	110±7	105±3	102±4	98±6	101±6	109±4
CZON	98±5	106±3	110±6	107±4	92±7	108±7	103±2
CMNX	107±4	106±2	110±4	108±6	100±3	104±2	109±6
CDZM	105±5	107±2	106±5	108±4	115±7	106±12	110±7
AZT	102±7	98±3	104±8	102±3	101±6	99±4	105±7
CRMN	107±6	101±10	106±6	103±5	108±3	96±5	102±2
IPM	105±6	102±5	108±7	107±4	101±7	102±3	109±9

Results are given as the percentage of the integral CL of cells without drug and represent the mean±standard error (m±SE) of six to seven experiments.

mum essential medium : pH 7.4, Ca^{2+}-and Mg^{2+}-free), and ajusted to a final concentration of 5×10^5 PMNs/ml in MEM. Two ml of whole blood was diluted with 8 ml of MEM for whole blood CL assay and stored on ice until use.

Measurement of chemiluminescence. The production of oxygen-derived radicals by phagocytes was measured by luminol-dependent CL assay. The reaction mixture contained 0.9 ml of leukocyte suspension (5×10^5 cells) or diluted whole blood (0.1 ml of whole blood+0.8 ml of MEM) for phagocytic cells, 0.1 ml of 0.9% saline (control : containing the same concentration of DMSO as the drug-treated sample) or 0.1 ml of antibiotic solution at various concentrations of 8~2,000 μg/ml.

After preincubation at 37°C for 10 min, zymosan (a particulate stimulus) or PMA (a soluble stimulus) was added to the mixtures and the CL was continuously measured for 20 min with a six-channel Biolumat LB 9505 (Berthold, FRG).

A chemiluminescence index (CL-index) was determined for each drug studied and defined as the mean difference in drug-treated CL/untreated CL (control).

Table 2. Effect of β-lactam antibiotics on PMN-CL stimulated with zymosan or PMA

Drug	Zymosan induced CL				PMA induced CL		
	concentrations (μg/ml)				concentrations (μg/ml)		
	1.6	50	100	200	1.6	50	100
PCG	101±3	102±3	106±3	110±4	104±3	106±2	103±5
ABPC	99±3	100±2	102±6	103±4	98±3	98±4	106±2
MCIPC	100±3	95±6	96±4	97±4	99±4	95±8	94±7
PIPC	98±2	92±7	95±7	96±4	102±2	97±2	98±3
ASPC	99±3	103±2	102±3	101±4	104±3	97±3	101±4
CEZ	100±3	102±3	99±4	98±4	99±4	103±3	101±2
CMD	97±3	106±4	103±5	99±4	102±7	92±8	103±6
CTM	99±2	100±3	104±5	104±2	99±3	96±4	97±6
CMZ	96±6	99±3	104±2	106±4	104±6	98±3	99±7
CTT	101±4	102±3	99±4	98±3	97±5	101±2	102±3
CBPZ	104±3	101±4	97±3	99±4	99±6	103±5	106±3
CTX	98±4	100±3	102±2	103±4	99±2	102±4	107±1
CZX	99±3	100±2	106±5	107±6	105±3	96±2	93±4
CMX	99±4	101±3	98±2	102±4	99±4	102±6	100±4
CPM	98±6	103±4	102±6	98±4	99±3	104±2	106±5
CAZ	97±4	104±3	102±4	100±2	102±4	98±5	103±4
CTRX	100±3	104±3	109±3	109±4	99±3	102±4	110±3
CPZ	109±4	99±6	99±7	98±4	96±4	99±6	101±7
CPIZ	97±5	104±9	111±8	112±7	100±4	109±4	112±9
LMOX	106±3	100±2	97±4	104±2	104±3	96±3	102±4
FMOX	102±4	96±3	98±6	101±4	98±4	100±3	108±4
CZON	100±4	98±6	104±5	98±3	99±4	105±6	96±8
CMNX	105±4	98±3	100±3	108±5	107±3	106±4	103±3
CDZM	96±7	98±6	117±6	110±7	107±4	108±5	108±4
AZT	98±4	100±2	92±7	93±6	104±6	98±5	100±4
CRMN	96±3	104±3	93±6	98±3	106±5	99±4	103±5
IPM	105±2	102±4	108±3	103±4	98±4	102±3	106±3

Results are given as the percentage of the integral CL of cells without drug and represent the mean±standard error (m±SE) of six to seven experiments.

Table 3. Effect of antibiotics on the CL response of whole blood or PMN stimulated with zymosan or PMA

Drug	Zymosan induced CL			PMA induced CL		
	concentrations (μg/ml)			concentrations (μg/ml)		
	1.6	50	100	1.6	50	100
Whole blood CL						
GM	103±6	103±1	103±4	103±4	99±6	103±6
TOB	97±3	94±5	105±5	99±4	106±7	106±7
AMK	106±2	101±3	102±2	103±3	99±6	98±4
HBK	100±2	101±2	95±4	99±3	98±2	103±2
EM	105±3	101±2	101±2	107±4	99±2	87±8
CLDM	105±4	105±4	107±3	105±2	106±2	102±3
FOM	103±2	99±6	98±3	98±3	109±6	108±2
VCM	101±1	102±1	109±3	103±1	104±2	110±6
PMN CL						
GM	104±5	106±7	99±2	109±7	104±4	97±3
TOB	108±4	110±7	110±5	92±8	98±5	108±5
AMK	109±6	108±6	107±6	101±4	103±3	103±3
HBK	99±2	103±2	104±5	97±3	101±3	101±2
EM	97±4	103±4	104±2	99±4	94±6	92±8
CLDM	103±3	94±7	98±6	102±3	99±4	95±4
FOM	97±6	100±3	99±4	102±3	103±5	102±4
VCM	106±2	97±4	100±3	100±4	96±2	104±4

Results are given as the percentage of the integral CL of cells without drug and represent the mean±standard error (m±SE) of six experiments.

Table 4. Effect of antifungal agents on the CL response of whole blood or PMN stimulated with zymosan or PMA

Drug	Zymosan induced CL				PMA induced CL			
	concentrations (μg/ml)				concentrations (μg/ml)			
	1.6	6.2	12.5	25	1.6	6.2	12.5	25
Whole blood CL								
AMPH	98±3	101±2	104±3	107±3	106±2	102±3	98±6	109±4
MCZ	109±6	103±4	110±7	108±3	101±4	97±3	99±5	95±6
5-FC	101±2	104±5	108±6	106±4	102±1	96±4	102±2	103±3
PMN CL								
AMPH	93±7	104±2	94±5	99±6	98±3	103±2	110±6	106±4
MCZ	100±3	109±2	101±2	109±5	108±4	106±4	109±6	110±7
5-FC	97±4	103±3	103±4	104±2	102±3	96±2	100±2	102±4

Results are given as the percentage of the integral CL of cells without drug and represent the mean±standard error (m±SE) of six experiments.

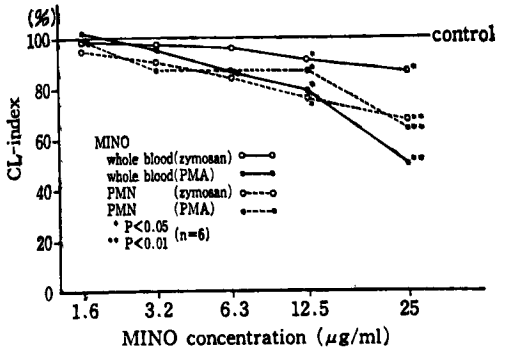

Fig. 1. Effect of minocyclin (MINO) on the CL response of whole blood or PMN stimulated with zymosan or PMA. The CL-index is given as the percentage of the integral CL of cells without MINO and represents the mean value of six experiments. The range was within 10% of the mean

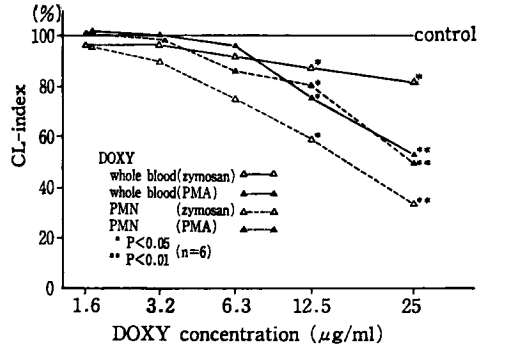

Fig. 2. Effect of doxycyclin (DOXY) on the CL response of whole blood or PMN stimulated with zymosan or PMA. The CL-index is given as the percentage of the integral CL of cells without DOXY and represents the mean value of six experiments. The range was within 10 % of the mean

This index was calculated by dividing the integral CL of drug-exposed phagocytes by the integral CL of untreated phagocytes.

Statistical analysis was performed using STUDENT's t-test.

RESULTS

Twenty-seven β-lactam antibiotics were assayed at final concentrations from 1.6～200 μg/ml by two-fold dilutions. After preincubation at these levels for 10 min, no significant influence on the CL response of PMN or whole blood was observed during 20 min after addition of zymosan or PMA (Tables 1, 2).

Four aminoglycosides such as GM, TOB, AMK, HBK and EM, CLDM, FOM, VCM were

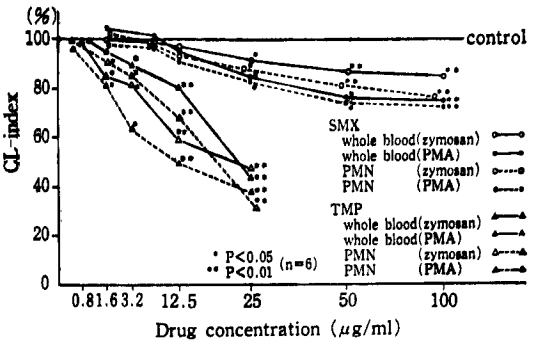

Fig. 3. Effect of sulfamethoxazole (SMX), trimethoprim (TMP) on the CL response of whole blood or PMN stimulated with zymosan or PMA. The CL-index is given as the percentage of the integral CL of cells without drug and represents the mean value of six experiments. The range was within 10% of the mean

tested at concentrations of 1.6～100 μg/ml. They had no effect on the CL response of phagocytic cells (Table 3).

AMPH, MCZ, 5-FC did not show any inhibitory effect on the CL response at concentrations of 1.6～25 μg/ml (Table 4). However, at concentrations of more than 50 μg/ml, which are therapeutically unachievable, AMPH significantly reduced the CL response of PMN (data not shown).

MINO and DOXY showed a statistically significant reduction in the CL response of PMN or whole blood at concentrations of more than 12.5 μg/ml.

However, the reduction was not found to be significant at concentrations below 6.2 μg/ml (Figs. 1, 2).

SMX and TMP had an inhibitory effect on the CL response at therapeutic concentrations of 25 μg/ml of SMX and 1.6 μg/ml of TMP (Fig. 3). This inhibitory activity was found to be dose-dependent.

DISCUSSION

When PMN and soluble or particulate matter (bacteria, zymosan, etc) come into contact, the cells respond with a burst of oxidative metabolism[4]. The generation of chemically reactive molecules [superoxide anions (O_2^-), hydrogen peroxide (H_2O_2) singlet oxygen ($^1O_2$), hydroxyl radicals (·OH), myeloperoxidase (MPO)-catalyzed reactions as a result of respiratory burst activation] is an essential step in host defense against microorganisms[10]. The production of these reactive molecules can be measured as light emission from the PMN[11]. This emitted light can be detected as chemiluminescence (CL), which is enhanced by the presence of luminol[12]. The luminol enhanced system permits the use of very few cells and can be

used to measure CL in samples of whole blood[13,14]. It suggests that light-generation in luminol-dependent CL is totally dependent on the MPO-H_2O_2 system[15].

A large number of reports have shown that several antimicrobial agents at therapeutic concentrations can inhibit some functions of phagocytic cells, including chemotaxis, uptake and killing of pathogenic organisms, and certain metabolic functions as measured by the CL response. However, conflicting data have been reported for these same agents[16]. In this report, we studied forty-two commonly used antimicrobial agents for their effect on the generation of luminol-dependent CL in human phagocytic cells *in vitro*. Phagocytes obtained from healthy volunteers were used for CL as whole blood or fractionated PMN, and zymosan or PMA was prepared for CL stimuli.

Many investigators have reported that most β-lactam antibiotics had very little direct effect on the various functions of phagocytic cells such as chemotaxis, phagocytosis, killing and metabolic response[2,7]. Our findings on the CL response of β-lactam antibiotics are in agreement with most reports, and there was no significant effect on the CL response of these drugs at therapeutic concentrations. Recently, AC-1370 (CPIZ), a new cephalosporin, has been reported to enhance chemotaxis, phagocytosis, intracellular killing and superoxide generation of human PMN *in vitro*[3]. However, we could find no significant enhancement in the CL response of human phagocytic cells in this study.

In the presence of TCs such as MINO or DOXY, whole blood CL and PMN-CL were inhibited at high concentrations of more than 12.5 μg/ml. Some investigators have reported inhibitory effects of TCs on some phagocytic cell functions: chemotaxis, bacterial uptake and chemiluminescence[6,17,18]. They have assumed that this inhibitory effect is based on good intracellular penetration and the divalent cation (Ca^{2+}, Mg^{2+}) chelating ability of TCs. Recently, Glette et al. have shown that DOXY or MINO impaired CL or glucose oxidation at concentrations of more than 10 μg/ml[19].

Siegel et al.[6] have reported that SMZ and TMP, individually and in combination, inhibit the CL of PMN in response to phagocytosis of *Candida albicans*. The inhibitory effect of these drugs was reversible, dose-dependent, and occurred at concentrations readily achieved in serum during therapy. Welch et al. have reported a study in which 19 antimicrobial agents were evaluated for their effect on PMN function, and TMP inhibited CL and reduced killing at a concentration of 20 μg/ml[16]. In our findings, SMX slightly inhibited the CL of both whole blood and PMN at concentrations of more than 25 μg/ml. TMP had the same inhibitory effects on CL at concentrations of more than 1.6 μg/ml. In this way, both drugs inhibited the CL of phagocytic cells at therapeutic concentrations even with two different stimuli.

Furthermore, a few antifungal agents, including AMPH, MCZ and 5 FC, have been examined for their effect on the CL of phagocytic cells. AMPH has been shown to inhibit PMN CL only at clinically unachievable high concentrations of more than 50 μg/ml, but no inhibition on the CL response of PMN or whole blood at concentrations of 1.6~25 μg/ml. MCZ and 5 FC did not show any reduction in CL at any tested concentration. BJÖKSTÉN et al. reported inhibition of the CL response after pretreatment of PMN with 5~20 μg/ml of AMPH and stimulation with opsonized zymosan[20]. On the other hand, Siegel reported no effect with AMPH at a concentration of 6.25 μg/ml on the CL response of PMN stimulated with opsonized *Candida albicans*[6].

In summary, most β-lactam antibiotics, AGs, EM, CLDM, FOM and antifungal agents (except high concentrations of AMPH) have no influence on the CL of phagocytic cells in our studies, but it seems likely that MINO and DOXY reduce CL at rather high concentrations of 12.5 μg/ml and SMX, TMP inhibits CL at therapeutic concentrations. Recently, patients with reduced immunological capabilities or neutropenia due to underlying diseases or some immunosuppressive therapies have increased. They are sometimes suffering from severe infections caused by various opportunistic pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), glucose-nonfermenting Gram-negative rods, *Pneumocystis carinii* or fungus. When administered to these immunocompromised patients, drugs that inhibit the CL response may further reduce or suppress the already-impaired antimicrobicidal activity[6]. The possible negative effects of some antimicrobial agents *in vitro* should not be ignored, especially in the treatment of these patients. To determine whether these *in vitro* results are significant *in vivo*, further investigation is required.

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42 抗菌剤の食細胞の化学発光に及ぼす影響

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化学発光 (chemiluminescence ; CL) は，貪食殺菌能の鋭敏な一指標である。42 抗菌剤の好中球や全血を用いたルミノール依存性 CL に及ぼす効果について検討した。

食細胞と種々の濃度の抗菌剤を 10 分間接触させた後に，非オプソニン化ザイモザンや，ホルボールミリステートアセテート (PMA) で刺激して 20 分間の食細胞の CL 反応を測定した。

治療域において，sulfamethoxazole (SMX) と trimethoprim (TMP) は有意に CL 反応を抑制した。

Minocycline (MINO) と doxycycline (DOXY) もまた，少し高い濃度 (12.5 μg/ml 以上) で CL 反応を抑制した。しかし，β-ラクタム剤 (27剤)，アミノ配糖体 (4剤)，erythromycin, clindamycin, fosfomycin, vancomycin および抗真菌剤 (3剤) は，治療域において CL を抑制しなかった。

また，いずれの抗菌剤も，我々の検討した中では食細胞の CL 反応を増強させるものはなかった。

これらの結果は，MINO, DOXY, SMX, TMP は，臨床的に食細胞の殺菌能を減じることを示唆している。特に，すでに殺菌能に異常を有している immunocompromised hosts における治療においては，*in vitro* で CL 反応を抑制するこれらの薬剤は，さらに食細胞の機能を減じたり抑制したりするかもしれない。しかし，これらの観察の臨床的意義についてはさらに今後の研究が必要である。

* 東京都板橋区加賀 2-11-1