The aim of this study was to assess the in vitro activity of Cefepime combined with Sulbactam against Carbapenem- resistant strains of Acinetobacter. spp clinical isolated. We used the checkerboard method to determine whether combinations act synergistically against these strains. 23 A. baumannii and one A. junii strains that were found to be Carbapenem- resistant were included the study. Isolates were collected from the specimens, blood, urine, sputum of patients from 2004 to 2005. All isolates were identified by VITEK- 2 system and stored at- 70℃ until use. The susceptibility results for Cefepime and sulbactam were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. P. aeruginosa ATCC 27853 and E. coli ATCC 25922 were used as quality control strains. The combination of Cefepime and sulbactam demonstrated 33. 3% (8/24) synergism, 58. 3% (14/24) partial synergism, 4. 2% (1/24) additive, 4. 2% (1/24) indifference, and no antagonism (Sigma FIC(min) = 0. 25 and Sigma FIC(max) = 1. 5)

According to our in vitro study results, Combinations of Cefepime with Sulbactam has moderate synergistic activity against some Carbapenem- resistant strains of Acinetobacter. spp which could be likely to prove beneficial for the treatment of infections due to multidrug- resistant strains of Acinetobacter. spp.

Key words: Cefepime, Sulbactam antimicrobials; Acinetobacter. spp; Carbapenem - resistant; synergy

P020031

The Tolerance of Gatifloxacin Mehanesulfanae after Single- Dose Intravenous Infusion in Chinese Healthy Volunteers

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OBJECTIVE To evaluate the safety and tolerance of gatifloxacin mehanesulfanae in Chinese healthy volunteers treated by single- dose intravenous infusion. METHODS The clinical trial protocol was designed according to the GCP principle after ethics committee passed. After physical examination and laboratory tests were performed, 48 healthy volunteers in 18~ 50 years old were divided into100mg 、200mg 、300mg 、400mg 、500mg 、600mg 、700mg and 800mg groups respectively by Latin method. Clinical symptoms, vital signs, blood routine et al were observed or examined before and after single- dose intravenous infusion of gatifloxacin mehanesulfanae. RESULTS It has shown that after single- dose intravenous infusion from 100mg to 800mg of gatifloxacin mehanesulfanae in the volunteers, the vital signs, clinical symptoms and laboratory tests were mainly in the normal range, only 3 cases of ADRs were found involved in the drug, such as pruritus, rash, GOT or GPT increasing slightly. CONCLUSION Chinese healthy volunteers treated by single- dose intravenous infusion up to 800mg of gatifloxacin mehanesulfanae were safe and tolerable.

P020032

Research of target genes mutant site of E. coli mutants selected in the MSW

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Objective To investigate the effect of drug concentration 、drug structure of fluoroquinolones on the resistant gene of E. coli mutants selected in the mutant selection window(MSW). Methods The target genes, gyrA and parC of E. coli mutants selected in the MSW were obtained by PCR method and sequenced by DNA sequencing. The agar dilution method was carried out to determine MIC of E. coli mutants. Results Among 53 mutants selected by five fluoroquinolones, 79% had a Ser- 83 —Leu mutation detected in the quinolone resistantdetermining region of the gyrA gene, 19% from Asp to a Asn residue at position 87, 2% from Gly to a Cys residue at position 81, and no parC mutation was detectable. MIC of mutation at position 83 was 2~ 8 fold larger than that at position 81 and 1~ 2 fold larger than that at position 87. Mutation at position 83 was the most important factor to influence the sensitivity of E. coli. DNA gyrase is the primary target, mutation at position 83 and 87 was the most frequent and no- target mutation was also involved in the resistance.

Conclusion DNA gyrase is the primary target of five fluoroquinolones against E. coli, mutation at position 83 and 87 was the most frequent.

P020033

The study on characteristics and dynamics of Escherichia coli during PAE determined by flow cytometry

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Objective The change of sizes and nucleic acid contents of Escherichia coli were studied during the Postantibiotic effect after exposure to gatifloxacin and ciprofloxacin in order to investigate the mechanism of PAE. Methods The aliquots were taken from the bacterial culture at regular interverals during postantibiotic effect after exposure to gatifloxacin and ciprofloxacin. The dynamic change of sizes and nucleic acid contents of Escherichia coli were determined by flow cytometry in conjunction with fluorescent probes. Results The sizes of Escherichia coli were different from those of the control population. In parallel, an increase in nucleic acid contents was still noted at the end of the experiment. This change was inhibited by the protein synthesis inhibitor Chloramphenicol and the RNA synthesis inhibitor Rifampicin. Conclusion: Gatifloxacin and Ciprofloxacin induced filamentation and the increase of nucleic acid contents of Escherichia coli was inhibited by the protein synthesis inhibitor and the RNA synthesis inhibitor. Flow cytometry is an ideal methodology for study of the PAE.

P020034

Mutant prevention concentration for four fluoroquinolones with Staphylococcus aureus and Escherichia coli

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OBJECTIVE: The mutant prevention concentration (MPC) and MIC against S. aureus and E. coli of ciprofloxacin, pazaufloxacin, gatifloxacin, moxifloxacin were determined and their potent to resitrict resistant mutants was compared. METHODS: For MPC testing, 1010 cells were applied to agar plates containing drug and incubated at 35℃ for 48~ 72h, the lowest concentration inhibiting mutant was difined as MPC. MPC90 was the concentration inhibiting 90% of mutant. RESULTS: MPCs of moxifloxacin, gatifloxacin, pazaufloxacin and ciprofloxacin to S. aureus ATCC 25923 were 0. 18, 0. 3, 0. 75, 1. 8ug/ml and MPC90 to clinical isolates of S. aureus of the four drugs were 1 、1 、4 and 8ug/ml respectively. MPCs to E. coli ATCC 25922 of moxifloxacin, gatifloxacin, pazaufloxacin and ciprofloxacin were 0. 072, 0. 048, 0. 09, 0. 06ug/ml and MPC90 to clinical isolates of E. coli (n= 20) were 1, 2, 1, 2ug/ml. MPCs of moxifloxacin and gatifloxacin against S. aureus and E. coli were 2~ 4 fold less than pazaufloxacin and ciprofloxacin CONCLUSION: The results suggested that moxifloxacin and gatifloxacin would be more effective to prevente selection of resistance mutant of S. aureus and E. coli than pazaufloxacin and ciprofloxacin.

P020035

Anti- Helicobacter pylori activity of three spcies of Lamiaceae family

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In this study, the anti- Helicobacter pylori activity of three species of Lamiaceae family, namely Zizphora cliniopodides, Thymus trancaspicus and Zataria multiflora grown wild in Iran against clinical isolates were investigated using hole plate method. The results indicated that the extracts exhibited inhibitory activity against most isolates. The activities are dose dependent and approaches that of metronidazole at about 200 mg/ml.

P020036

Synthesis of conformationally restricted analogues of pentamidine as antileishmanial agents

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Our groups are interested in the design and evaluation of novel bisbenzamidines that are more efficient and less toxic than the parent compound, pentamidine(1) with oral bioavailability. With that goal in mind and based on previous works we considered 1 as a bisbenzamidine in which both benzamidine moieties are linked by a flexible pentamethylene chain and activated by electron- donating ether functions. We studied the influence of the linking chain by reducing its flexibility. We also replaced the strong electron- donating ether functions present in 1 with poor electron donating groups, namely amides. So, series of conformationally restricted analogues of pentamidine in which the flexible central bridge has been replaced by pyridinyl- 3, 5- dicarbamido, or pyrazolyl- 3, 5- dicarbamido groups were synthesized. Treatment of 4- aminonenzamidine with pyrazole or pyridine 3, 5- dicarbonyl halides afforded the title compounds (2, 3). The synthesized compounds pKa compared to 1 is greater and so better penetration through cell membranes are expected. As amastigote forms of leishmania parasite are intracellular, we suppose more potency and better oral absorption for the title compounds.

P020037

Restoration of antibiotic susceptibility of methicillin- resistant *Staphylococcus aureus* by blocking blaR1 with a DNAzyme

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AIM: To investigate the effects of DNAzyme inhibiting Methicillin- resistant Staphylococcus aureus (MRSA) drug- resistant gene blaR*1* on the expressions of MRSA drug- resistance. METHODS: Specific DNAzyme to blaR*1* mRNA was designed and synthesized. After DNAzyme was introduced into MRSA, drug- resistant characters of MRSA were evaluated by plate cloning formation experiment. The inhibition effects of DNAzyme on the expressions of drug- resistant gene blaR*1* and its downstream gene blaZ were observed by real time RT- PCR. RESULTS: Colony forming units(CFU) of MRSA incubated with DNAzyme on the M- H agar added oxa(6 mg/l) were less than those of control group($P< 0.01$). Levels of blaR1 and blaZ mRNA of the DNAzyme groups were lower than those of the control group. CONCLUSION: Antibiotic sensitivity on MRSA may be partially restored by DNAzyme which blocks the expressions of drug- resistant genes blaR*1* - blaZ. This provided a new idea for development gene drugs to resist other drug- resistance bacteria and diseases.

Key words: Methicillin- resistant Staphylococcus aureus (MRSA); DNAzyme; drug- resistance; real- time fluorescence quantitation.

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P03. Cancer Chemotherapy

P030001

Protective effects of L- arginine against cisplatin- induced renal oxidative stress and toxicity: Role of nitric oxide.

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Nephrotoxicity is a dose- limiting factor in clinical use of cisplatin. The aim of the present study was to investigate the effect of modulation of nitric oxide on cisplatin- induced Nephrotoxicity in a rat model. A nitric oxide precursor, L- arginine and a competitive inhibitor of NO synthase, L- NAME were used. Six days after cisplatin injection, acute nephrotoxicity was demonstrated by a marked increase in serum creatinine and blood urea. Histological examination confirmed the occurrence of renal damage. Moreover, cisplatin induced an increase in lipid peroxides and oxidized glutathione and a depletion of reduced glutathione. Activities of antioxidant enzymes glutathione peroxidase and superoxide dismutase were lowered. Besides, there was a reduction in kidney total nitrate/nitrite levels. L- arginine attenuated the oxidative stress and the nephrotoxic effect of cisplatin while. L- NAME aggravated cisplatin nephrotoxicity. In conclusion, the decrease in kidney nitric oxide level contributes, at least in part, in the mechanism underlying the nephrotoxicity of cisplatin. Furthermore, Larginine provides nephroprotective effects and might be useful in improving the therapeutic index of cisplatin.

P030002

Antiproliferation in human EA. hy926 endothelial cells and inhibition of VEGF expression in PC- 3 cells by topotecan

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To investigate the mechanism of the antiangiogenesis activity of TPT, series of experiments were performed. We found that TPT inhibited proliferation of human EA. hy926 endothelial cells (IC_{50} value was 0.13 μM in MTT assay), and exhibited high inhibitory activity of angiogenesis in chick embryo chorioallantoic membrane assay. DNA analysis confirmed that TPT could trigger EA. hy926 cells apoptosis in a dosed- dependent manner, and cause disturbance of cell cycle, inducing G2/M phase accumulation at a dose of 0.05 μM, G1/G0 phase accumulation at a dose of 5.0 μM, and S phase accumulation at a dose of 0.5 μM. Western Blotting showed that overexpression of p53 and downregulation of ERK caused by TPT were observed in EA. hy926 cells, and the VEGF expression of PC- 3 cells was inhibited by TPT in hypoxia. Altogether, inhibiting proliferation of endothelial cells and down- regulating the expression of VEGF in cancer cells involved in the antiangiogenesis mechanism of TPT.

Key word: Topotecan; Antiangiogenesis; EA. hy926 cells; VEGF.

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P030003

MZ3 Induces Apoptosis in Human Leukemia Cells through Mitochondrial Pathway

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MZ3 exhibited high anticancer activity in six leukemia cell lines (IC50 $1.2 \times 10^{-8.0}$M), including two drug- resistant cell lines. MZ3- induced DNA fragmentation in HL60 cells was observed with a dose- dependent and time- dependent manner. An elevation of reactive oxygen species was also observed in HL60 cells treated with $10^{-8.0}$M MZ3 at 2 h, and a loss of mitochondrial membrane potential was detected at 8 h. The protein changes related to mitochondrial dysfunction indicated that MZ3 induced the activation of caspase- 3, influenced the expression of Bcl- 2 family members, MAPKs and other proteins relative to apoptosis. Furthermore, the anticancer activity in vivo was evaluated on SCID mice model of human leukemia engrafts. A prolonged survival time of MZ3 group (MST 33.5 days) was observed after treatment with MZ3 compared with the MST (15 days) in the control group. Together, our data suggested that MZ3 is a potent compound against leukemia cell lines both in vitro and in vivo, and the mitochondrial pathway mediated by Bcl- 2 protein family and MAPKs might be involved in signaling MZ3- induced apoptosis.

Key Words: leukemia, Bcl- 2 protein family, MAPKs, caspases, mitochondria

P030004

Antiproliferative activity of Fenretinide in human heptoma cells in vitro and in vivo

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To evaluate the anticancer activity of fenretinide against hepatoma cells both in vitro and in vivo and the potential mechanisms. Fenretinide exhibited high efficiency on cell growth inhibition of Bel- 7402, HepG2 and Smmc- 7721 in vitro with IC_{50} values 12.5- 13.9mM, measured by MTT method. We used flow cytometry to analyze the ratio of apoptotic Bel- 7402 cells induced by 15.0mM fenretinide for 0- 48 h, with results ranging from 3% - 48% respectivelv. In a Bel- 7402- xenografted athymic mice model, administrations i.p. once per three days with fenretinide (25.0- 100.0mg/kg) for 21 days significantly inhibited tumor growth and the inhibition rates ranged from 37.2% to 57.2%. By western blotting, downregulation of procaspase- 3, XIAP and cleaved PARP were observed in Bel- 7402 treated with 15.0 mM fenretinide for 48 h. In addition, overexpression of p53 was in atime- dependent manner, along with the decrease of the ratio of Bcl- 2/Bax. Fenretinide effectively inhibited the proliferation of Bel- 7402 both in vitro and in vivo, and p53 and procaspase- 3 mediated apoptosis pathway was involved in its potent anticancer mechanisms.

Key words: Fenretinide; hepatoma cells; apoptosis; xenografted