Editorial

Resistance of Pseudomonas aeruginosa to Imipenem

Harold C. Neu, MD, FACP

The manuscript by Gaynes and colleagues from the Hospital Infections Program of the Centers for Disease Control (CDC) [1] on resistance to imipenem of selected gram-negative bacilli points out a resistance problem that was anticipated for imipenem when the drug was first introduced worldwide.[2] The basic questions to answer are how common is the problem, will it become worse, and why does it occur?

Imipenem is a most interesting and unique compound that belongs to the class of agents called carbapenems.[3,4] In its current form, there has been marked chemical modification of an agent that began as thienamycin, was modified to n-formidoyl thienamytin, and now clinically is used as imipenem combined with a dehydropeptidase inhibitor cilastatin. Imipenem inhibits gram-positive and gram-negative bacteria and aerobic and anaerobic species.[4] It binds to specific penicillin-binding proteins (PBPs)-PBP-2-and causes rapid death of bacteria. It is extremely b-lactamase stable and has an unusual property of causing a post-antibiotic effect on gram-negative species as well as on gram-positive species, unlike most b-lactam antibiotics. Imipenem is a small molecule, and as such, it diffuses through the outer membrane of bacteria by distinct outer membrane porin channels. In ***Pseudomonas aeruginosa,*** imipenen overcomes the poor outer membrane permeability of b-lactams for ***Pseudomonas*** by penetrating through protein D2.[5,6]

Acar,[2] in his review of the use of imipenem in the initial worldwide clinical trials of imipenem, noted that ten of 54 (18.5%) of ***P aeruginosa*** strains became resistant to imipenem, and nine new imipenem-resistant strains of ***P aeruginosa*** developed in 47 patients. In spite of the selection of resistant strains, ten of 16 patients showed clinical improvement. Unfortunately, we do not know the severity of illness of the patients or whether the patients were in intensive care units. Salata et al[7] at the University of Virginia also reported on the development of resistance to imipenem of ***Pseudomonas*** respiratory isolates. Quinn et al[s] reported that resistance to imipenem, which developed during therapy, was caused by a lack of outer membrane protein D2, and Buscher et al[9] had a similar finding that protein D2 was absent. Trias et al[10] showed that at low concentrations, the specific channel is saturable and not enough imipenem reaches the PBPs.

Studies in 1989 from Japan by Goto and colleague@ showed that imipenem-resistant ***P aeruginosa*** from clinical laboratories in Japan lacked the D2 outer membrane protein. Interestingly, the moderately susceptible or moderately resistant, depending on one's viewpoint, strains that had imipenem minimum inhibitory concentrations of 6.25 mg/ml produced trace amounts of protein D2. Strains of this type are susceptible to a new carbapenem: meropenem, which is currently undergoing clinical evaluation. Highly imipenem-resistant ***P aeruginosa*** is resistant to meropenem and to another carbapenem LJC 10,627, which is being evaluated in Japan. The explanation for the difference in susceptibility of meropenem and imipenem for the relatively resistant strains appears to be from chromsomal b-lactamase production, which is better induced by imipenem than by meropenem.[12] It also appears that other b-lactams can select ***P aeruginosa*** with stably derepressed b-lactamase production, and when these isloates lose protein D2 they become highly resistant to imipenem.[12] The small amount of hydrolysis of imipenem combined with the lack of an adequate number of molecules reaching the PBPs makes the organism resistant. Whether, as suggested by Kahan and colleagues,[3] ceftazidime resistance

From the Division of Infectious Diseases/Epidemiology, Department of Medical, College of Physicians & Surgeons, Columbia University, New York, New York.

Address reprint requests to Harold C. Neu, MD, FACP Division of infectious Diseases/Epidemiology, Department of Medicine, College of Physicians & Surgeons, Columbia University, 630 West 168 St., New York, NY 10032.

Neu HC. Resistance of Pseudomonas aeruginosa ***to imipenem.*** Infect Control Hosp Epidemiol. *1992;13:7-9.*

appeared before the imipenem resistance, or, as suggested in the report in this issue,' that imipenem and ceftazidime resistance were associated, remains an unsolved issue. It is likely that resistance to other p-lactams such as the antipseudomonas penicillins also was present in the imipenem isolates, because these drugs often are used before imipenem is used. It is important to realize that isolated resistance to imipenem can develop in ***P aeruginosa*** strains that will remain susceptible to piperacillin and to ceftazidime. Indeed, if imipenem was the sole agent used in an intensive care unit, such imipenem-resistant ***Pseudo***-mas would be the organism seen.

Knowing the molecular basis of the resistance to imipenem, could we prevent it by some mechanisms? It has been postulated that use of two different antimicrobial agents, a p-lactam and an aminoglycoside, will prevent the emergence of resistance. In unpublished studies in our institution, using aminoglycosides plus imipenem in intubated intensive care patients with respiratory infection caused by ***P*** aeruginosa did not prevent the development of resistance. We also have seen resistance of ***Pseudomonas*** to imipenem develop in patients with cystic fibrosis who were treated with imipenem and tobramycin. Thus, I do not believe that combinations of agents will prevent development of resistance.

Is the resistance reported by Gaynes et al real? I believe that the 25% increase in resistance in teaching hospitals has occurred over the four-year period, and I suspect that with time there will be further increases in imipenem resistance of ***P aeruginosa.*** As noted in the beginning of this editorial, imipenem is an extremely useful agent. It is a reasonable agent to treat multiply resistant bacteria, which ***P aeruginosa*** frequently are. Unforunately, the intensive care unit patient who develops a serious respiratory infection frequently does not rapidly improve clinically, often has an indwelling nasotracheal or orotracheal airway, and has poor clearance of large numbers of bacteria. This is the ideal setting in which to develop resistance to any class of antibiotic. Resistance of ***P aeruginosa to*** b-lactams, aminoglycosides, and recently to fluoroquinolones has developed in this clinical situation of respiratory infections.[14] Excess and, above all, inappropriate use of an agent such as imipenem to treat oral or tracheal Pseudomonas-colonized patients is a perfect way to cause resistance. The difficulty in making a diagnosis of what is causing fever in intensive care unit patients results in an excessive use of antibiotics.

Gaynes and colleagues' noted that there has not been an increase in resistance of ***Enterobacter*** species to imipenem. This is in contrast to the increased resis***tance*** of ***Enterobacter*** to cephalosporin antibiotics.[15] The reason is that ***Enterobacter*** has a much lower possibility of developing reduced permeability than does ***Pseudomonas.*** Recently, Lee and colleague@ from Paris described a clinical isolate of ***Enterobacter cloacae*** that had reduced outer membrane permeability and high-level production of b-lactamase. Furthermore, Raimondi et al[7] showed that laboratory strains of ***E cloacae*** that produce very high levels of b-lactamase and diffusely loose porins can be made highly resistant to imipenem and meropenem. Fortunately these strains do not appear to be very stable, and when the exposure to the carbapenem is removed, susceptible bacteria return. This would indicate that stopping the use of imipenem in a unit where one saw resistant ***Enterobacter*** should result in return to susceptibility We may see such imipenem-resistant ***Enterobacter*** isolates over the next few years, and, as Gaynes et al[1] points out, these isolates may not be as readily detected by the current surveillance techniques.

It is clear from the study reported in this issue that we must follow the use of imipenem in the hospital, particularly in intensive care units. Close attention should by given to the frequency of cross infection of intensive care unit patients with the imipenem-resistant isolates. It is not established whether the membrane-deficient ***Pseudomonas*** are as virulent as imipenem-susceptible isolates or whether the resistant isolates colonize patients as readily as other strains. It should be possible to investigate this and determine the exact magnitude of the problem. It is not established if the use of other b-lactams initially select for isolates that are more likely to lose the D2 protein. The resistance seen in the very early trials of imipenem when patients had not received other antibiotics suggests that this is not a factor but it should be investigated.

Unforunately, resistance to bacteria such as ***Pseudomonas*** and ***Enterobacter*** species will not vanish. The types of patients who develop infections from these organisms, the procedures that occur in intensive care units, and the amount of time that critically ill patients remain in intensive care units all predispose to resistance development. Critical evaluation of antibiotic use combined with measures to reduce nosocomial infection will hold the problem in check. This means that there must be continued evaluation of the use of agents such as imipenem in intensive care unit patients if we will retain this excellent antibiotic and have it available for those situations where it is life-saving.

REFERENCES

1. Gaynes RP: Culver DH, National Nosocomial Infections Surveillance System. Resistance to impenem among selected gram-negative bacilli in the United States. *Infect* Control *Hosp Epidemiol.* 1992;13:10-14.
2. Acar JF Therapy for lower respiratory tract infections with

imipenem/cilastatin: a review of worldwide experience. Rev *Infect Dis.* 1985;7(suppl 3):513-517.
3. Kahan JS, Kahan FM, Goeglman et al. Thienamcyin, a new b-lactam antibiotic. I. Discovery, taxonony, isolation, and physical properties. *J Antibiot (Tokyo).* 1979;32:1-12.
4. Birnbaum J, Kahan FM, Kropp H, MacDonald JS. Carbapenems, a new class of b-lactam antibiotics. *Am J* Med. 1985;72(suppl 6A):3-21.
5. Trias J, Nikaido H. Outer membrane protein D2 catalyzed diffusion of carbapenems and penems through the outer membrane of *Pseudomonas* aeruginosa. *Antimicrob Agents Chemothel:* 1990;34:52-57.
6. Satake S, Yoshihara E, Nakae T. Diffusion of b-lactam antibiotics through liposome membranes reconstituted from purified porins of the outer membrane of *Pseudomonas* aeruginosa. *Antimicrob Agents Chemother:* 1990;34:685-690.
7. Salata RA, Gebhart RL, Palmer DL, et al. Pneumonia treated with imipenem/cilastatin. *JAMA.* 1985;78(suppl 6A):96-102.
8. Quinn JP, Dudek EJ, Di Vencenzo CA, Lucks DA, Lerner SA. Emergence of resistance to imipenem during therapy for *Pseudomonas aeruginosa* infections. *J Infect Dis.* 1986;154:289-294.
9. Buscher KH, Cullmann W, Dick W, Opferkuch W. Imipenem resistance in *Pseudomonas* aeruginosa resulting from diminished expression of an outer membrane protein. *Antimicrob Agents Chemother* 1987;31:703-708.
10. Trias J, DuFresne J, Levesque RC, Nikaido H. Decreased outer membrane permeability in imipenem-resistant mutants of *Pseudomonas aeruginosa. Antimicrob Agents Chemother:* 1989;33:1201-1206.
11. Goto M, Goto S, Shimada K. Frequency of isolation of *Pseudomonas aeruginosa* in 19 domestic hospitals and their drug susceptibility. Proceedings of the Annual Meeting Japanese Society Chemotherapy. Tokyo, Japan 1989. #232.
12. Satake S, Yoneyama H, Nakae T. Role of Omp D2 and chromosomal b-lactamase in carbapenem resistance in clinical isolates of *Pseudomonas aeruginosa. J Antimicrob Chemother:* 1991;28:199-207.
13. Kahan FM, Drusano GL, ISS Study Group. Resistance of gram-negative organisms isolated from ICU patients in four cities to b-lactam antibiotics. Presented at the Third Decennial Conference on Nosocomial Infections. July 31-August 2, 1990. Atlanta, Ga. #66.
14. Parry ME Pazer KB, Yokna ME. Quinolone resistance: susceptibility data from a 300-bed community hospital. Am *J Med.* 1989;87(suppl 5A):12-16.
15. Sanders CC. Editorial: new b-lactams: new problems for the internist.Ann *Intern Med.* 1991;115:650-651.
16. Lee EH, Nicolas MH, Kitzis MD, Pialoux G, Collatz E, Gutmann L. Association of two resistance mechanisms in a clinical isolate of *Enterobacter cloacae* with high-level resistance to imipenem. *Antimicrob Agents Chemother:* 1991;35:1093-1098.
17. Raimondi A, Traverso A, Nikaido H. Imipenem- and meropenem-resistant *Enterobacter cloacae* and *Proteus rettgeri* lack porins. *Antimicrob Agents* Chemother: 1991;35:1174-1180.