Impact of dosage regimens on the efficacy of antibiotics in the immunocompromised host

The schedule of drug administration may play an important role in the outcome of antibiotic treatment of serious infection, particularly in the immunocompromised host, as in these patients recovery from infection depends to a high degree on antibiotics, and therapeutic failure still occurs. It is not clearly established whether or not repeated high antibiotic serum concentrations of short duration are superior to continuously maintained antibiotic serum concentrations at lower level.

Vogelman & Craig (1986) described a number of important determinants for optimal dosage regimens. In relation to the half life of a drug, the rate of bacterial killing as well as the postantibiotic effect (PAE) appear to be important factors. The PAE means the suppression of bacterial growth that persists after a limited exposure of the bacteria to an antimicrobial drug (Craig & Gudmundsson, 1985). Differences in PAE are observed for different antibiotic-pathogen combinations. In general, β-lactams produce PAE with Gram-positive cocci, but give very short or no PAE with Gram-negative bacilli. Aminoglycosides and also quinolones induce PAEs of moderate to long duration with both Gram-positive and Gram-negative bacteria. The PAE may be an important factor in the case of intermittent dosing with antibiotics. Regarding the bacterial killing rate, it appears that the in-vitro antibacterial activity of aminoglycosides is in general strongly dependent on the antibiotic concentration, and is in addition very rapid. β-Lactams differ in this respect from aminoglycosides in that their antibacterial effect in vitro is less concentration-dependent, but is more related to the duration of active antibiotic levels (Vogelman & Craig, 1986). Quinolones also exhibit concentration-dependent bactericidal activity. In addition bacterial killing by quinolones is extremely rapid. These in-vitro data suggest that therapeutic efficacy for β-lactams depends mainly on the time that bacteria are exposed to effective antibiotic concentrations, whereas for aminoglycosides or quinolones efficacy is mainly dependent on the value of the peak concentration of the antibiotic.

As clinical trials especially in immunocompromised patients are difficult to perform, experimental infection models in animals have been used extensively to study the impact of dosage regimens on the therapeutic efficacy of antibiotics. Experimental studies in animals with intact host defences yielded somewhat contradictory results. The discrepancies observed in individual studies may be explained by differences in the infection model, in the virulence of the bacterial strains, and in the mode or duration of antibiotic administration. More consistent results have generally been obtained by investigators studying infections in animals with impaired host defences. A better understanding of the role of antibiotic dose schedules in relation to the therapeutic efficacy in the immunocompromised host may be of great importance. Therefore only experimental studies in animals with impaired host defences will be discussed here.

In experimental pneumonia and septicaemia caused by Klebsiella pneumoniae in leucopenic rats the therapeutic efficacy of different dose schedules of ceftazidime, administered either intermittently at 6-h intervals, or by way of continuous infusion, during a period of four days, was compared (Roosendaal et al., 1986). Continuously maintained serum concentrations of ceftazidime appeared to be far more effective than relatively high peak concentrations in serum at 6-h intervals. That the bactericidal effect of ceftazidime is not strongly dependent on the peak concentration, as suggested by these findings, was confirmed by experiments in which the effect of different doses of ceftazidime administered as a single intravenous injection upon the numbers of bacteria in the lungs of leucopenic rats was determined. The data show that bacterial killing in the lung was not dependent on the dose administered, although the peak concentrations in serum obtained varied from 50 mg/l to 1 mg/l. Regarding dose schedules of β-lactams, Gerber et al., (1986) came to a similar conclusion using a thigh muscle infection model caused by Pseudomonas aeruginosa in leucopenic mice. In these experiments mice were treated with ticarcillin either as a single bolus injection or, at the same total amount of drug, in fractional doses at 15-min intervals. In terms of decrease in bacterial numbers at the site of infection administration in fractional doses at 15-min intervals was far superior to administration as a single bolus injection, which resulted in bacterial regrowth as soon as the ticarcillin
plasma level fell below the MIC. Similar results were obtained for the \( \beta \)-lactam cepazidime. Using the same infection model, Gerber et al. (1983, 1984) also demonstrated superior efficacy of ticarcillin when administered at 1-h intervals rather than at 3-h or 4-h intervals. Similarly, in experimental thigh infection caused by \( K. \) pneumoniae in leucopenic mice Gudmundsson, Turnidge & Craig (1982) demonstrated that ceferazone administered at 1-h intervals reduced the bacterial numbers at the site of infection to a greater extent than the same antibiotic every 4 h.

In a model of intraperitoneal infection by \( P. \) aeruginosa in neutropenic rats Mordenti, Quintiliani & Nightingale (1985) showed that ticarcillin administered every 30 min resulted in reduced mortality, as compared with untreated controls, whereas administration at 3-h intervals did not. Investigations using experimental infections caused by Gram-positive bacteria led to similar observations. As demonstrated by Gerber, Bundtzen & Craig (1981) and Craig (1984) the bacterial count in the thigh of leucopenic mice infected with \( S. \) pneumoniae was more effectively reduced by injecting penicillin at 1-h intervals than by administration every 4 h. In a model of pneumococcal pneumonia and septicaemia, in rats with impaired phagocytosis, penicillin G administered by continuous infusion was more effective in sterilizing the lungs than dosing at 8-h intervals (Bakker-Woudenberg et al., 1984). So in general it may be concluded that the therapeutic effect of \( \beta \)-lactams in immunocompromised animals is not strongly peak-level dependent, but depends mainly on the time an appropriate drug level is maintained.

In this respect aminoglycosides differ from \( \beta \)-lactams. In the model of \( K. \) pneumoniae pneumonia and septicaemia in leucopenic rats the therapeutic efficacy of gentamicin, administered either continuously or at 6-h intervals, was not much influenced by the dose schedule (personal unpublished results). The observation that at the same total daily dose gentamicin was about equally effective when administered continuously or at 6 h intervals, suggests that the bactericidal effect of gentamicin is dependent on the peak concentration. Intermittent administration at relatively long intervals seems to be permitted without loss of efficacy. That the bactericidal effect of gentamicin is dependent on the peak concentration was confirmed by our observations that the bacterial killing in the lungs of leucopenic rats after a single intravenous injection was dependent on the dose administered. These results are in agreement with those of Gerber et al. (1983, 1986) and Brugger, Gerber & Feller-Segessenmann (1983) who compared different dosage schedules of gentamicin or netilmicin in the thigh model of infection with \( P. \) aeruginosa in leucopenic mice. The same total amount of the aminoglycoside was administered at different intervals ranging from 5 min up to 12 h. With the different dosage schedules no differences in efficacy in terms of decrease in bacterial numbers at the site of infection were observed. So in general from the experimental studies with aminoglycosides it may be concluded that in contrast to \( \beta \)-lactams, the therapeutic activity of aminoglycosides in the immunocompromised animals is dependent on peak concentrations in plasma.

Regarding the quinolones up to now only few data are available on the impact of the dosage regimen on the therapeutic activity. In our hands the therapeutic effect of ciprofloxacin as measured in the \( K. \) pneumoniae pneumonia and septicaemia model in leucopenic rats was not strongly influenced by the dosing schedule, but the 6-h regimen was slightly more effective than administration by continuous infusion (unpublished results).

The data derived from the experimental infection models may have implications for the treatment of human infections. For successful treatment with \( \beta \)-lactams of severe infections, particularly in the immunocompromised patient, it is of great importance that antibiotic concentrations are maintained at a certain level during the period of treatment. High peak concentrations in serum do not contribute to a therapeutic effect. In terms of cost-effectiveness total daily doses may be lowered provided antibiotic is administered more frequently or continuously, or \( \beta \)-lactams with long half lives are used. In addition increased efficacy of \( \beta \)-lactams in immunocompromised host may be achieved. Regarding aminoglycosides and quinolones there is no experimental evidence that the dose schedule is an important determinant for efficacy. In view of the fact that the bactericidal effect of these antibiotics is strongly dependent on the dose, and the bacteria killing is very fast, intermittent administration at relatively long intervals seems permissible without loss of efficacy. More studies are needed to investigate whether less frequent dosing with slightly increased doses may be equally effective in the immunocompromised host. In this respect the data of Powell et al. (1983) derived from studies in dogs and in patients with cystic
fibrosis are of great interest, showing that intermittent dosing of aminoglycosides, causing infrequent relatively high serum concentrations, may be less toxic than and equally efficacious as frequent dosing.

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Antimicrobial resistance in Branhamella catarrhalis

Until the 1970s Branhamella catarrhalis was considered a harmless commensal of the upper respiratory tract causing isolated cases of meningitis, endocarditis and septicaemia (Kallings, 1986). Recent studies, however, have demonstrated a marked increase in the occurrence of B. catarrhalis in middle-ear exudates of children with acute otitis media (Kovatch, Wald & Michaels, 1983; Shurin et al., 1983) and respiratory secretions from predominantly elderly patients with infection secondary to underlying pulmonary disease (Ninane, Joly & Kraytman, 1978; McLeod et al., 1983; Slevin, Aitken & Thomley, 1984). In these reports were suggestions that B. catarrhalis has become more virulent; however, specific virulence factors, such as IgA protease, have not been identified (Mulks & Plaut, 1978; Van Hare et al., 1987).

It is difficult to tell whether the increase in incidence of B. catarrhalis infections is real. In several investigations there have been minimal changes in isolation rate during three to four year study periods, and this suggests increased awareness rather than increased incidence (Davies & Maesen, 1986; DiGiovanni et al., 1987), although comparable data from periods predating these studies would be required to clarify this point. An important factor may be the recent emphasis on the ability of diagnostic laboratories to identify B. catarrhalis correctly (Doern & Morse, 1980), and to distinguish it from non-fermentative 'non-pathogenic' Neisseria spp. such as N. cinerea and N. flavescens (Knapp et al., 1984; Vedros,
1984). It is no longer acceptable to rely on the lack of fermentation of glucose, lactose, sucrose and maltose to identify these organisms. Additional tests such as nitrate and nitrile reduction, tributyrin hydrolysis and utilization of 5% sucrose to form polysaccharide (Vedros, 1984; Riley, 1987) should be employed. It is of interest to note that there has been an increase in resistance to colistin in some strains of *B. catarrhalis* resulting in their being able to grow on modified Thayer-Martin medium (Doern & Morse, 1980; Corkill & Makin, 1982) and reinforcing the requirement for accurate identification.

Clearly there has been a rapid increase in the rate of isolation of β-lactamase-producing strains of *B. catarrhalis*. Early studies showed the majority of strains to be highly susceptible to penicillin (Barber & Waterworth, 1962; Kamme, 1970). In 1977 several publications focused attention on the ability of *B. catarrhalis* to inactivate penicillins (Malmvall, Brorson & Johnson, 1977; Percival et al., 1977) and since then β-lactamase production in these organisms has been reported with increasing frequency (Doern et al., 1980; Kovatch et al., 1983; Ahmad et al., 1984). In our laboratory, at the end of 1982, 36% of *B. catarrhalis* isolates were β-lactamase producers, while by the end of 1984 the incidence had increased to 90%. All strains remained uniformly susceptible to tetracycline and resistant to trimethoprim, while susceptibility to erythromycin, sulphamethoxazole and co-trimoxazole varied slightly (DiGiovanni et al., 1987), in agreement with earlier findings of Doern et al. (1980), Brorson, Axelsson & Holm (1983) and Stobberingh, Davies & Van Boven (1984). We recently examined the susceptibility of *B. catarrhalis* to sulphamethoxazole, trimethoprim and co-trimoxazole in some detail (Riley, DiGiovanni & Hoyne, 1987). The optimum ratio of sulphamethoxazole to trimethoprim for synergy was either 1 : 1 or 1 : 2, although the commercially available 20 : 1 ratio was still effective *in vitro*. Although the penetration into respiratory secretions of both components of co-trimoxazole is not good, and subinhibitory concentrations can occur, a suitable ratio for synergy may still be achieved. Certainly in-vivo experience suggests that co-trimoxazole is efficacious for respiratory tract infections due to *B. catarrhalis* (Burman, 1986). Suitable alternatives include erythromycin and, in adults, tetracycline (Kallings, 1986), while the combination of clavulanic acid with amoxycillin has been shown to be effective (Wallace et al., 1985; Van Hare et al., 1986).

β-Lactamase inhibitors such as clavulanic acid may be important when *B. catarrhalis* is acting as an indirect pathogen. In some studies isolates of *B. catarrhalis* from sputum and middle ear effusions were mixed with more traditional respiratory tract pathogens such as *Haemophilus influenzae* or *Streptococcus pneumoniae* or both (Shurin et al., 1983; Slevin et al., 1984). Although the β-lactamases of *B. catarrhalis* are predominantly cellbound (Farmer & Reading, 1986), the potential exists for sufficient enzyme to be released to contribute to treatment failures. They are, however, particularly susceptible to inhibition by clavulanic acid. Thus, with increasing evidence of tetracycline resistance among isolates of *S. pneumoniae* (Jacobs et al., 1978), β-lactamase inhibitors, combined with penicillins may be useful in such mixed infections.

The β-lactamas found in *B. catarrhalis* are different from those of other bacteria, such as *H. influenzae* and *N. gonorrhoeae*, which produce TEM-1 enzymes. At least two distinct types of β-lactamase have been identified in *B. catarrhalis*. The Ravasio enzyme (Farmer & Reading, 1982) has been found in the majority of strains (Stobberingh et al., 1984; Van Hare et al., 1987) and appears to be similar to the BRO-1 enzyme described in Sweden (Eliasson & Kamme, 1985). The enzyme from strain 1908 was distinguishable from that of the Ravasio strain by isoelectric focusing and differences in substrate and inhibition profiles (Farmer & Reading, 1982). The report by Stobberingh et al. (1984) also describes three additional β-lactamases not commonly found in other surveys (Nash et al., 1986).

The rapid increase in incidence of β-lactamase-producing strains led to speculation that β-lactamase production in *B. catarrhalis* was plasmid-mediated; however, most attempts to demonstrate this have been unsuccessful (Percival et al., 1977; Doern et al., 1980; Stobberingh et al., 1984; Pintado et al., 1985). Swedish workers have described conjugal transfer of a β-lactamase gene, specifying BRO-1, between *Branhamella* strains and also from *Moraxella liquefaciens* to *B. catarrhalis* (Kamme, Vang & Stahl, 1983; 1984). However, excessive nuclease activity did not allow conclusive characterization of extrachromosomal DNA. Other problems in the procedure were that the resistance determinant appeared very unstable and was lost unless potential donor cells were subcultured on to
penicillin-containing medium immediately after primary isolation, and the fact that transconjugants so obtained could not act as secondary donors (Kamme et al., 1983). Subsequent refinements in the procedures have allowed the identification of extrachromosomal DNA; however, plasmids of similar size were detected in both β-lactamase-positive and -negative strains (Kamme et al., 1986). Conclusive evidence of plasmid-mediated β-lactamase production in B. catarrhalis is still required. Attempts to transform a suitable recipient with DNA preparations have also been unsuccessful, presumably again because of excessive nuclease production. Hence it seems unlikely that, in general, the emergence of β-lactamase-producing B. catarrhalis is related to the spread of a plasmid, although the possibility of a transposable element cannot be discounted.

The question remains, therefore, why there has been such a rapid increase in β-lactamase-producing B. catarrhalis. Several theories have been advanced. The first relates to the widespread use of trimethoprim, both alone and in the form of co-trimoxazole, in the treatment of respiratory tract infections. B. catarrhalis is intrinsically resistant to trimethoprim owing to the production of a dihydrofolate reductase (Then, 1979) and it has been suggested that trimethoprim therapy may select out strains of B. catarrhalis that are both trimethoprim resistant and β-lactamase producers (Calder et al., 1986). Lacey et al. (1980), however, could find no evidence of selection of resistant strains after trimethoprim therapy and a more likely selective pressure is the use of β-lactam antimicrobials. Another possibility is that there has been an as yet undetermined changed in virulence of strains of B. catarrhalis which is in some way linked to β-lactamase production.

An interesting point was raised by Calder et al. (1986) who reported that in 1983 53% of their patients apparently acquired B. catarrhalis infections while in-patients, suggesting nosocomial spread within the hospital environment. In vitro experiments demonstrated the survival of B. catarrhalis for several weeks in sputum (McLeod et al., 1986) although the organism’s resilience has been known for some time (Wilson & Miles, 1964). Further investigations, including the development of a typing scheme, are required to determine the role of B. catarrhalis in nosocomial infection.

Whether as a direct or indirect pathogen the presence of B. catarrhalis in clinical specimens should be reported. The ability of any isolate to produce β-lactamase should be determined so that appropriate antimicrobial chemotherapy can be instituted if required.

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