Leading articles

β-Lactamase induction and resistance to β-lactam antibiotics

Certain Gram-negative bacilli, including Enterobacter, Citrobacter and Providencia spp., Morganella morganii, Serratia marcescens and Pseudomonas aeruginosa produce a β-lactamase of the Class I type and the production of this enzyme in these bacteria is typically inducible; that is to say, enzyme production is normally held at a low level by a repressor mechanism, but in the presence of a β-lactamase inducer this repression is lifted and enzyme production is greatly increased (Hennessey, 1967; Richmond & Sykes, 1973; Sykes & Matthew, 1976).

Many penicillins and cephalosporins can function as β-lactamase inducers; some of these compounds are good inducers and some are poor inducers, while others appear not to function as inducers at all. The efficiency of induction depends not only on the compound itself but also on the species and strain of bacterium and on the concentration of the inducer present. Induction is essentially a temporary phenomenon; so long as the inducer is present the level of enzyme synthesis is increased but when the inducer is removed the level of enzyme production returns to the original level.

If a penicillin or cephalosporin functions as an inducer the increased level of β-lactamase may result in an increased rate of inactivation of the antibiotic but this does not have any long-term consequences and it does not lead to the development or the emergence of stable resistance in the strain, following therapy. However, in pathogens that produce Class I β-lactamase, resistance can emerge clinically following β-lactam therapy; this is the result of selection of resistant mutants within the population that produce high levels of Class I β-lactamase constitutively (Findell & Sherris, 1976; Lampe et al., 1982). These mutants are referred to as derepressed mutants because they lack the repressor mechanism (Lindberg, Westman & Normark, 1985) and can produce high levels of β-lactamase regardless of the presence or absence of a β-lactamase inducer.

As a result of stable high level β-lactamase production these mutants are resistant to a wide range of penicillins and cephalosporins including third generation compounds (Gootz & Sanders, 1983; Gwynn & Rolinson, 1983). Derepressed mutants occur at a high frequency in Enterobacter spp. and in Ps. aeruginosa and can be selected out during β-lactam therapy, particularly when the β-lactam antibiotic is one which is not a strong inducer and not highly stable to the enzyme. Under these circumstances the derepressed mutants have a selective advantage (Simon et al., 1980; Shannon, King & Phillips, 1982; Sanders & Sanders, 1983). Emergence of resistance in a clinical sense therefore is a matter of selection of resistant mutants and not the result of induction. Does induction nevertheless, have clinical relevance?

If a penicillin or a cephalosporin is a β-lactamase inducer, but is not highly stable to the enzyme produced, the increased level of β-lactamase may result in a more rapid rate of inactivation of the antibiotic than otherwise would have been the case and in this way the activity of the antibiotic will be diminished. Ampicillin for example is a good inducer of β-lactamase synthesis in E. cloacae and this factor is largely responsible for the low level of activity that this penicillin shows against most strains of this species. β-Lactamase induction may also have clinical relevance when double β-lactam therapy is employed. If a strong inducer is used concomitantly with a labile weak inducer the former may bring about an increased rate of inactivation of the latter, the effect being one of antagonism. Cefoxitin and imipenem for example, which are strong inducers, can antagonize the activity of third generation cephalosporins and ureidopenicillins. However, this does not lead to emergence of resistance; the result at the worst will be failure of therapy in the individual patient due to an increased rate of inactivation of the labile compound.

The proprietary double β-lactam formulations of amoxycillin or ticarcillin with clavulanic acid (Augmentin or Timentin) thus raise the question of possible antagonism. Clavulanic acid, however, is only a weak inducer of Class I β-lactamase (Moosdeen, Keeble & Williams, 1986; Aronoff & Shlaes, 1987; Farmer & Reading, 1987; Then, 1987)
and as far as the amoxycillin/clavulanic acid formulation is concerned, the antibiotic component (amoxycillin) does not have any important clinical place in the treatment of infections caused by the organisms which produce Class I $\beta$-lactamase. In the case of ticarcillin and clavulanic acid, antagonism can be demonstrated in vitro for certain strains of bacteria which produce Class I $\beta$-lactamase (King, Gransden & Phillips, 1983; White et al., 1987) but this is not always very reproducible and in studies in which groups of Class I $\beta$-lactamase producers have been tested for susceptibility to ticarcillin compared with ticarcillin plus clavulanic acid the proportion of strains susceptible to the combination has proved to be similar or somewhat greater than the proportion susceptible to ticarcillin alone (Casey & Glauser, 1983; King et al., 1983; Barry et al., 1984; Clarke & Zemcov, 1984; Bansal, Chuah & Thadepalli, 1985; Pulverer, Peters & Kunstmann, 1986; Verbiest & Verhaegen, 1986; Stobberingh, 1988).

In summary it can be said that certain bacteria including Enterobacter spp. and Ps. aeruginosa typically produce a $\beta$-lactamase inducibly but that such cultures also frequently contain a minority population of mutants which produce the same type of $\beta$-lactamase at a high level constitutively and it is the selection of these derepressed mutants that is responsible for the emergence of resistance in the clinic, not the phenomenon of $\beta$-lactamase induction.

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References
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The chemotherapeutic approach to zoster

Zoster is a common disease. Population-based cohort studies have shown incidence rates of 1.3–3.4 per thousand population per year (Hope-Simpson, 1965; Ragozzino et al., 1982). Hope-Simpson calculated that 50% of people reaching the age of 85 years will have suffered zoster and 1% will have had more than one attack. The incidence rises sharply with advancing years, possibly owing to a decline in cellular immunity, with post herpetic neuralgia (PHN), the major complication of zoster, being more common in the older group. Figures for PHN vary according to the population studied, but differences also occur between apparently similar groups studied by different workers. Pain persisting for more than six months after acute zoster has been reported as occurring in 45–6% of one cohort of 430 patients over the age of 60 years (de Moragas & Kierland, 1957). In contrast, in 164 patients over 60 years studied in Sheffield only 34 (21%) still had some pain at six months, and only eight (5%) of these had moderate or severe pain (personal observations).

Zoster is readily identified clinically once the rash appears and the astute physician may make the diagnosis before the onset of the rash, from the dermalonal distribution of pain which is characteristic in the prodromal illness. Many remedies have been used in zoster and there is much folklore surrounding the illness. Most, such as acupuncture, photodynamic inactivation, stellate ganglion block and amantadine have no proven efficacy; some, such as corticosteroids, remain controversial.

Antiviral therapy offers a logical approach to the treatment of the acute infection and the prevention of the PHN even though the pathogenesis of this condition has not been established. Histological changes may occur in the posterior root ganglion and peripheral nerve in some patients following zoster and it is a reasonable hypothesis that effective antiviral therapy early in the course of the acute illness will limit viral replication and hence may reduce inflammation and pain. Assessment of antiviral agents in zoster has been based on observations on the rash and the pain, on virus isolation during the acute illness, and on PHN. Adenine arabinoside, interferon and idoxuridine have all shown some effect in modifying the acute illness, although an effect on PHN has not been proven with any of these agents at the conventional dosages (Whitley et al., 1976; Merigan et al., 1978; Wildenhoff et al., 1981). All have the common disadvantage of toxicity.

Acyclovir has been established as an effective, well tolerated and non toxic oral therapy for the treatment and prophylaxis of herpes simplex infections. Varicella zoster virus (VZV) is less sensitive than herpes simplex virus by a factor of about ten. The steady state peak serum concentrations of acyclovir following intravenous doses of 5 mg and 10 mg/kg 8-hourly exceed the effective median dose (ED 50) of most strains of VZV. Serum concentrations are lower after oral administration of similar dosage as only 15–20% is absorbed. Nonetheless, the steady state peak and trough concentrations of 7.5 and 4.5 μmol/l, respectively, obtained with a dose of 800 mg 4-hourly exceed the ED 50 of the majority of strains of VZV (unpublished findings).

Studies of intravenous acyclovir (10 mg/kg, 8-hourly) in immunocompromised patients have shown benefit in decreasing cutaneous