quinolones in general practice? It should and must not be the widespread use of these compounds based on their wide activity against most bacterial species, and the unavailability of bacteriological services. In all instances there must be a high index of clinical suspicion suggesting that the patient has an infection due to a resistant organism. Where possible it should be reserved for infections due to known resistant strains, with certain exceptions such as cystic fibrosis, chronic urinary tract infections and catheter-associated infections. The use of quinolones as prophylactic agents in travellers' diarrhoea requires further study, but the treatment of patients with established infective gastroenteritis would appear to be a sound clinical indication. The quinolones should not be used for mild infections such as tonsillitis, acute uncomplicated cystitis and acute or chronic bronchitis, particularly where established therapies exist and are effective.

A new group of antimicrobial agents with enhanced activity against bacterial infection and easier administration should be carefully used for the benefit of society. Although a pharmaceutical company has committed many of its resources to the development, clinical trial and marketing of a newly developed compound and is entitled to recover this expenditure, it is incumbent on the company to provide appropriate advice regarding its prescription. The quinolones represent a major step in the development of antimicrobial compounds, but their market life will be related to careful usage and it would be a tragedy if inappropriate and thoughtless prescribing led to a lessening of their value in the treatment of bacterial infection.

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Activity of glucosidase inhibitors against HIV infections

Most success to-date in the treatment of the Acquired Immunodeficiency Syndrome (AIDS) has been achieved with inhibitors of reverse transcriptase. The use of azidothymidine (AZT) has provided clinical benefits to

patients with advanced disease and some clinical efficacy has been observed for a second nucleoside analogue, dideoxycytidine. Both drugs can induce serious side-effects with potential for long-term use being restricted, but other nucleoside derivatives are being investigated. Alternative targets for the chemotherapy of HIV infections are under consideration such as protease activity involved in the processing of viral proteins, anti-sense oligodeoxynucleotides to complement essential viral genes and post-translational events such as myristylation or glycosylation (subjects to be reviewed in the Journal's supplement on AIDS and related infections; Bint & Oxford, 1988). In relation to the latter target, the antiviral properties of a series of polyhydroxyalkaloids against the growth of human immunodeficiency virus (HIV) *in vitro* have recently been described (Gruters *et al.*, 1987; Tyms *et al.*, 1987; Walker *et al.*, 1987; A. Karpas, unpublished data). These natural substances, which accumulate in plants and microorganisms but can also be synthesised, bear a structural resemblance to monosaccharides. Three different structural types are active, namely polyhydroxy derivatives of octahydroindolizine (castanospermine; CAST), piperidine (deoxynorimycin; DNJ) and pyrrolidine (dihydroxymethyldihydroxypyrrolidine; DMDP) (reviewed by Fellows, 1986). These compounds are characterised by their ability to inhibit glucosidase activities involved in the trimming of the oligosaccharide side-chains of glycoproteins. The first step in the synthesis of *N*-linked sugars in mammalian cells involves transfer of the glycan component of a lipid-glycan intermediate to asparagine residues on the nascent polypeptide chain. The initial structure of the branched glycan of *N*-linked glycoproteins is *N*-acetylglucosamine 2 mannose 7-9 glucose 3. Subsequent modification involves the removal of the outermost glucose residue by glucosidase 1 (α1,2 linkage) and the two remaining glucose residues by glucosidase 11 (α1,3 linkages). This is a prerequisite of any further modification of the glycan moiety in the Golgi region by mannosidases, other glycosidases and transferases leading to hybrid and complex-type oligosaccharides (Fuhrmann, Bause & Pleogh, 1985; Martinez & Barsignian, 1987). CAST and DMDP both inhibit glucosidase 1 (Elbein *et al.*, 1984; Fellows, 1986) and DNJ inhibits glucosidase 1 and 11 (Saunier *et al.*, 1982; Fuhrmann, Bause & Pleogh, 1985).

The external glycoprotein of HIV (gp120) is the major surface component by which the virion attaches to CD4(T4) cellular receptors on helper T-cells (Dalgleish *et al.*, 1984). The envelope gene of HIV 1 encodes a precursor glycoprotein gp160 which is cleaved to produce gp120 and gp41, a transmembrane glycoprotein (Muesing *et al.*, 1985; Ratner *et al.*, 1985; Robey *et al.*, 1985; Veronese *et al.*, 1985). The gp120 is heavily glycosylated with up to 24 *N*-linked glycosylation sites (Muesing *et al.*, 1985; Ratner *et al.*, 1985). The expression of this glycoprotein on the surface of the host-cell after infection is responsible for cell fusion and syncytium formation (Lifson *et al.*, 1986) and this may contribute to the loss of CD4+ cells in AIDS (Barnes, 1986; Lifson *et al.*, 1986).

Treatment of HIV-infected T-cells *in vitro* with CAST, DNJ or DMDP at concentrations of 1 mM or more had a profound effect on the production of syncytia and virus growth (Gruters *et al.*, 1987; Tyms *et al.*, 1987; Walker *et al.*, 1987). The specificity of this effect was shown by using CD4+ cells constitutively expressing the HIV *tat* gene and transfected with a plasmid containing the *art* and *env* genes of HIV 1 (Sodroski *et al.*, 1986). The spontaneous production of large syncytia in these cells displayed a dose-dependent inhibition when exposed to CAST (Walker *et al.*, 1987). In contrast, deoxymannojirimycin (DMJ) (Gruters *et al.*, 1987) which blocks the cleavage of α 1,2 mannose residues by inhibiting mannosidase 1 or swainsonine (Montefiori, Robinson & Mitchel, 1987), which prevents the removal of α 1,3- and α 1,6-linked mannose residues by α–mannosidase 11, were both ineffective against HIV. As indicated by lectin binding studies (Lifson *et al.*, 1986), these results support the notion that oligosaccharides of the high mannose-type present on gp120 are critical for correct interaction with the host-cell. Extracellular levels of HIV from CAST-treated cells were similar to untreated controls, when measured by reverse transcriptase or p24 antigen assays but infectivity was reduced (Walker *et al.*, 1987). It appeared, therefore, that the retention of glucose residues on the surface glycans of HIV (Gruters *et al.*, 1987; Walker *et al.*, 1987) interferred with the infectivity. However, incorrect trimming of glucose residues is also known to affect the cleavage of precursors and intracellular transport of glycoproteins and this can alter their surface expression.

Our recent studies with human cytomegalovirus (CMV) have also shown major reductions in the infectivity to particle ratio in

infected cells treated with CAST (> 1 mM) which clearly correlated with an altered expression of viral glycoproteins on the virion surface (Taylor *et al.*, 1988). In this case, evidence points to the non-cleavage of a precursor glycoprotein when the glucose residues are retained on the glycan moiety. Similarly, a block in proteolytic cleavage of the Sindbis virus precursor E2 protein after treatment with methyl–DNJ accounted for the loss of extracellular virus (McDowell *et al.*, 1987) and was consistent with earlier observations made with vesicular stomatitis virus (Schlesinger, Malfer & Schlesinger, 1984) and mouse hepatitis virus (Repp *et al.*, 1985).

CAST, DNJ and DMDP were well tolerated in cell culture at concentrations with antiviral activity but only limited studies have been conducted on toxicity. The injection of young rats with CAST (up to 2000 mg/kg/ip) daily for three days induced diarrhoea suggestive of an inhibitory effect against gut glycosidases (Saul *et al.*, 1985). This was eliminated when animals were fed a simple diet based on glucose rather than complex carbohydrates although the inhibitory activity of 500 mgs/kg on α-glucosidases found in the liver and other organs was not reversed. In another study, the LD_{50} for CAST in mice was also greater than 500 mg/kg (Sunkara *et al.*, 1987). Evidence for the non-toxic nature of polyhydroxyalkaloids in man was provided when derivatives of DNJ were used to control Type II diabetes (up to 200 mg/day orally for three days). The medication was well tolerated with no apparent side effects (Joubert, Bam & Manyane, 1986; Schnack *et al.*, 1986). Further information on toxicity and antiviral activity of glucosidase inhibitors *in vivo* should come from the study of retroviral infections in animal models. Treatment with either CAST or DNJ was recently shown to inhibit the growth *in vitro* of Moloney murine leukaemia virus (MoLV). In agreement with studies on HIV, neither of the mannosidase inhibitors, DMJ or swainsonine, showed antiviral activity against MoLV (Sunkara *et al.*, 1987).

Enough is known about the antiviral activity of glucosidase inhibitors to warrant serious preclinical studies. Essential supplies of the natural compounds are scarce although synthetic substitutes may alleviate this problem. Derivatives of the presently available compounds are currently being investigated with the aim of identifying more potent agents with greater specificity for viral glycoprotein processing. Minor changes in the chemical structure of polyhydroxyalkaloids has already been shown to be important in influencing the antiviral activity (Tyms *et al.*, 1987; Taylor *et al.*, 1988).

Finally, if altering the oligosaccharide structure of virion glycoproteins proves to be an effective antiviral strategy in AIDS, then it may be beneficial to use compounds in combination that have different target enzymes.

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