PHMB - Summary for the Infection Control Fraternity

How the Unique Method of Action Precludes some Antiseptics from Resistance

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In recent years there has been some questioning of the potential of antiseptic residues, accumulating within high use environments such as clinics and hospitals, to select for bacteria that are altered with respect to their susceptibility (resistance) not only towards other antiseptics but also towards third party agents such as antibiotics. This summary looks to present a balanced discussion of various antibacterial agents, their method of action against selected bacteria and a discussion of their potential resistance development. Included in this presentation is an examination of the polymeric biguanide (PHMB).

Debate has been particularly heated with respect to the antimicrobial molecule triclosan that shares a common target (an enoyl reductase) with the anti-tubercular drug isoniazid. While it is now recognized that each agent attacks different elements of the enoyl reductase and that no cross-resistance is likely to be conferred, the debate has caused us to question the utility and safety of all antibacterial molecules. Other aspects of resistance development relate to the expression by most bacteria of multi-substrate efflux pumps. When induced, or hyper-expressed, such pumps remove antibacterial molecules and antibiotics from the cytoplasm (cell wall) and reduce their effectiveness. Since single pumps can often remove a selection of diverse molecules then it can be argued that selection of hyper-expressing efflux mutants through the use of antiseptics might compromise antibiotic use where the antibiotic is also a substrate.

The utility of cationic antimicrobial agents to combat cross infection is undeniable, as is the overall contribution of antisepsis to the reduction of hospital-acquired (nosocomial) infection. Indeed, reductions in antibiotic use brought about by such policies can be argued to have had a positive impact upon antibiotic resistance development. Examples of such use include improved localized skin site care, hand washing and hospital disinfectant procedures.

Nevertheless an examination of all antibacterial molecules destined for routine use in a clinical and domestic setting is appropriate. Cationic antimicrobials have been widely deployed in antisepsis for well over half a century without any apparent reduction in their effectiveness. They remain the mainstay of routine chemical antisepsis. Amongst the commonly deployed cationic antimicrobials are the quaternary ammonium based molecules (QAC, cetrimide, benzalkonium chloride), bisbiguanides (chlorhexidine) and polymeric biguanides (PHMB - Vantocil). All of these positively charged molecules bind strongly to the cell wall and membranes of bacteria because of their opposite, negative charge. It is important to note, that the nature of the interaction with the cell following this binding determines activity and the potential for resistance development and that this differs between the major classes of agent.

QAC have been in use since the turn of the 20th Century and have not suffered any reductions in their effectiveness during this time. QAC's have never been as effective

against Gram-negative bacteria such as *Pseudomonas aeruginosa* as they have been against Gram-positive bacteria such as Staphylococci. Indiscriminate use of QAC will therefore tend to enrich for Gram-negative bacteria. This is not generally a problem in the environment since such bacteria, unlike the Gram-positives, cannot survive dryness.

QAC molecules have a superficial resemblance to the phospholipids that comprise the major part of bacterial membranes, in that they possess a single positively charged region associated with a fatty-acyl side chain. Upon exposure to bacterial cells they integrate rapidly into the exposed side of the membrane with the positive group bound to particular phospholipid head groups. Since neither the membrane lipids nor the QAC's are able to move from one side of the membrane to the other, then this integration results in a distortion of the membrane bilayer and eventually cell lysis. Differences in susceptibility to QAC relates to the presence of an additional, outer membrane in Gram-negative bacteria, and changes in the relative abundance of the acidic-phospholipids that represent the preferred initial binding site to the membrane. Additionally, some efflux pumps (i.e. qac pumps) are able to selectively remove QAC from the membrane core thereby reducing their impact upon membrane integrity. Whilst such pumps do not affect the activity of QAC at use concentrations, they can bring about reductions in MIC towards third party antibiotics.

While other cationic antimicrobials share many aspects of their mechanism of action with QAC, bisbiguanides and polymeric biguanides are unaffected by the expression of efflux pumps. This is because they possess two or more positively charged groupings that confine the biocide to the surface of the membrane. Bisbiguanides (two positive groupings separated by a hydrophobic chain) therefore bridge together two adjacent acidic-phospholipids. The spacing between the positively charged guanidines is such that the bound phospholipids are forced apart, bringing about a similar distortion of the membrane as is demonstrated by QAC. Efflux pumps can only remove biocidal molecules that are present within the hydrophobic core of the membrane and are therefore ineffective against all of the biguanides. Biguanide activity is therefore unaffected by the efflux status of the target cells and will not select for hyperexpressing mutants. Polymeric biguanides (PHMB) such as vantocil add a further dimension to this action in that they represent long chain polymers comprising of many biguanide groupings each separated by an appropriate hydrophobic chain. PHMB's are superior to the bisbiguanides (CHG) because their binding to the cell membrane is multivalent and results in the sequestration of acidic phospholipids into a singular domain. Their high molecular weight makes them inappropriate substrates for efflux pumps.

Such attributes contribute to the excellent antimicrobial spectrum of activity for the polymeric biguanides (PHMB – Vantocil; Cosmicil) and make them a perfect adjunct for applications in hygienic wound care.