Photodynamic medicine and infection control

Mark Wainwright*

School of Pharmacy & Biomolecular Sciences, and Pharmalucia Ltd, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK

*Tel: +0151-231-2039; E-mail: mark_wainwright@hotmail.com

Given the problem of increasing antimicrobial—especially antibacterial—drug resistance and the paucity of new agents, it is sensible to consider alternative approaches to infection control to aid in conservation. Photantimicrobials are highly active agents, regardless of the conventional drug resistance status of the intended organism. Their use in infection control, via topical or local treatment protocols, has thus far received far from proper assessment and requires a wider audience.

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The four Leading articles by Wise,1 Livermore,2 Finch3 and White4 in the September issue of JAC made interesting and sobering reading. Quite correctly, they pointed out the parlous—and worsening—state of the available ammunition against our pathogenic foes and the receding prospects for ‘next generation’ antimicrobials.

The fact is that we must conserve our effective antibacterial agents, while maintaining infection control. On the face of it, this may seem something of a Catch-22 situation, but this pertains only if the argument is confined to conventional antimicrobial chemotherapy. Consequently, changes need to be made to the way in which we approach the treatment of infectious disease. Conservation of the small number of antimicrobials still useful in serious illness is imperative, so alternative approaches must be found to deal with ‘lesser’ conditions. In turn, this will require the re-education of the public and, indeed, many in the healthcare sector. One such approach is discussed below.

Imagine an antimicrobial molecule that is equally unaffected by such bacterial defences as β-lactamases (including extended-spectrum β-lactamases, KPCs etc.), penicillin-binding proteins and mutated topoisomerase and ribosomal targets. Similarly, imagine that the same molecule can be used as easily against Gram-positive, Gram-negative, viral or fungal targets. Finally, imagine that the time required to kill the microbial target is massively shortened, compared with conventional agents.

This is not imagination. The preceding paragraph describes a photoantimicrobial agent.

There is, of course, an added consideration. The molecule in question requires light activation in order to work these wonders. This means that it is useful for topical or local rather than systemic administration. However, this should not be an insurmountable problem—therapeutic illumination is already routinely employed in the treatment of conditions such as psoriasis and vitiligo, as well as in the related photodynamic therapy of various malignancies.

The science behind photoantimicrobial agents is relatively straightforward—indeed, simpler than the plant photosynthesis we all take for granted. However, where plants store light energy via carbohydrate synthesis, photoantimicrobials utilize it to fuel chemical reactions producing reactive oxygen species (ROS) such as the hydroxyl radical or singlet oxygen.5 These are highly damaging to microbial cells, and since the selectivity of the photoantibiotics used for such cells is great (e.g. methylene blue, which is used as a bacterial stain), a high therapeutic index is possible. In addition, local or topical application has the advantage of avoiding toxicity to the internal flora often encountered with oral antibacterials.

Light activation may be seen as a problem here, but this is not the case: focused illumination after local application of the photoantibacterial ensures a targeted, local rather than systemic, response. More difficult presentations, such as infection of the lungs or colon, are accessible via endoscopic means.

As mentioned, photoantimicrobials produce ROS on illumination. Analogues of basic dyes (such as methylene blue or toluidine blue) stain bacteria, fungi, viruses and protozoa grossly, and will be taken up by such cells non-specifically, to an extent that depends on the quantity of photoantimicrobial present and the contact time. For this reason, illumination (usually with a laser or, more commonly today, with cheaper, light-emitting diode devices) leads to microbial damage, which is also non-specific in terms of organelle/biostucture/biolecules, e.g. outer membrane and DNA in Escherichia coli, and reverse transcriptase, core proteins and RNA in HIV-1.5 This has clear ramifications in terms of selective pressure/resistance development. For the photoantimicrobial approach, a significant advantage lies in the lack of microbial resistance to reactive oxygen species. Given the state of our antimicrobial armamentarium, this is significant indeed.

To take an obvious example, drug resistance in E. coli can include AmpC, extended-spectrum β-lactamase and NDM-1 capability. However, none of these could cause any inhibition of the
ROS produced during photosensitization. Neither would other conventional resistance mechanisms, such as target alteration or drug inactivation. Even exclusion from the cell by efflux pumps, or decreased bacterial cell permeability would be ineffective, as illumination of the excluded photoantibacterials would then cause oxidative damage at the exterior of the cell—it has been established that photosensitizers immobilized within a polymer film exert a bactericidal effect on surface illumination.6

For the same reasons, future conventional resistance mechanisms are most unlikely to present a problem. There are many areas in which a directed, photoantimicrobial approach could be beneficial in terms of conservation of conventional antimicrobial drugs. For example, it has been trialled in skin and soft tissue infections such as acne7 and is licensed for use in oral disinfection.8 Work is also ongoing aimed at local methicillin-resistant Staphylococcus aureus decolonization, and the therapy of venous ulcers. To underline the antimicrobial utility of the approach, successful clinical outcomes (all using methylene blue) have been reported in cases of osteomyelitis, onychomycosis and herpes simplex lesions.9

The extension of this to other areas of infection (e.g. urinary tract and respiratory tract infections) depends on the acceptance of these initial forays by healthcare clinicians and regulatory bodies of course, and this would be helped in no small degree by the involvement of large pharmaceutical companies.

As noted above, the clinical use of photoantimicrobials will require some alteration in approach, e.g. in the application of light to the infection site. However, this is likely to be set out in standard protocols, as for other areas of therapy. It is envisaged that medical staff would be involved in treatments where an invasive procedure is required or a large topical area is involved. Again, depending on the anatomy, this might entail clinicians or nursing staff. For example, oral/nasal disinfection could be carried out by a general practice nurse, whereas organ involvement would require a specialist clinician, at least in endoscopy, siting the fibreoptic etc. More trivial presentations (e.g. onychomycosis) might be self-treated by the patient, using a metered illumination source tailored for the photoantimicrobial.

Photoantibacterials constitute a potentially powerful range of agents that could be employed both against conventional antibacterial resistance, and in the replacement/conservation of routine antibacterial regimens, where a topical/local approach is possible. However, their use requires greater clinical testing. The lead compound in this area, methylene blue, has a suitable human toxicity profile, being used routinely in malignancy tracing and the treatment of methaemoglobinemia, in both cases at hundreds of times higher concentration than that required to kill bacteria. Several other photoantimicrobial compounds, already in daily human use in other areas of medicine, have been suggested for use in skin and soft tissue infections.10

There is no single answer to the problem of our dwindling antimicrobial drug resources. Unfortunately, the influence of regulatory bodies and financial markets on healthcare and large pharma mean that, in many cases, it is prohibitively expensive to move a promising agent through the various required stages to the clinic. However, given the continuing rise of conventional drug resistance, promising alternatives surely deserve proper consideration. The use of methylene blue might be considered to be ‘old technology’, but photoantibacterials represent a 21st century application and brand-new agents are available—usually developed by academic spin-offs and small/medium enterprises (SMEs), both from dyes such as methylene blue and also from porphyrins and phthalocyanines11,12—with significantly higher activities. Greater investigation is required at the pre-clinical and clinical stages, otherwise we will not be able to make a rational choice.

References