



In Focus

Antibiotic Development and the Evolving Role of Pharmacodynamics — As Good as It Gets?

Glenn S. Tillotson^{a,*}, Stephen H. Zinner^b^a Transcrip Partners LLC, Downingtown, PA 19335, United States^b Department of Medicine, Mount Auburn Hospital, Cambridge, MA, United States

Antibiotic resistance has been declared one of the greatest threats to human health in both the developing and Organisation for Economic Co-operation and Development (OECD) nations. As pan-resistant strains of common pathogens are being transported around the world, it is clear that new antibiotics are needed. The current focus is on multi-drug resistant (MDR) Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, but there are many other similarly clinically challenging species. Many reviews and editorials have highlighted the recent lack of new antibiotics, and the causes of this situation are multifactorial but may lie in two or three areas: namely regulatory uncertainty, poor economic evaluations and potentially even local “bad governance” (Collignon et al., 2015). Although the US Senate approved the GAIN Act in 2012, it did not provide the agency with all the necessary tools to ensure new candidate agents could be reviewed using different, potentially quicker and less costly methods. New additional legislation is currently being reviewed by the US Senate, but until that is approved, some impediments to antibiotic development remain.

The year 2014 witnessed a plethora of new antibiotics gaining approval in the USA, but most were for Gram-positive pathogens [tedizolid (Sivextra), dalbavancin (Dalvance) and oritavancin (Orbactiv)], mainly active against methicillin-resistant *Staphylococcus aureus* (MRSA) with only ceftolozane–tazobactam (Zerbaxa) and ceftazidime–avibactam (AVYCAZ) approved for infections caused by Gram-negative pathogens. Current candidates in development for Gram-negative infections include plazomicin, meropenem-RPX70092 (Carbavance), S-649266 and several others.

These programs are still fairly conventional in design but perhaps could be accelerated with the use of additional studies of a pharmacological nature. Moreover, it is evident that as soon as we begin using a new drug or class, the bacteria begin to evolve mechanisms to resist its activity. This can show up as clinical resistance in five to twelve or more years but nevertheless the bacteria have this innate ability to put us back on the starting blocks.

We will describe some pharmacological approaches that could help slow the inevitable drive to resistance, but we seem unable to totally avoid this outcome. Perhaps integrating these concepts could provide new insights into how antibiotics work actually at the site of infection.

To date, we have focused all of the standard analyses of in vitro and in vivo activity using a fixed inoculum and pH setting. The use of 10^5 colony-forming units (CFU)/ml as the usual convenient inoculum does not bear much resemblance to the actual number of bacteria known to be present in infections. For example, it has been established that urinary tract infection occurs at bacterial concentration of 10^6 CFU/ml while Frisch et al. (1942) defined pneumococcal pneumonia occurring with inocula up to 10^{12} CFU/ml. This vast difference in initial inoculum demonstrates the “convenience” of current standard methods.

Clearly this number of bacteria and attendant inflammatory molecules and cells create a protein and immunoglobulin rich environment, which is rarely replicated in our models. It is evident that certain antibiotics are more heavily protein-bound than others, and it is the different activities in the rather false man-made conditions upon which we decide doses and regimens of these critically important drugs. Tschabitscher et al. (Tschabitscher et al., 2008) termed these drugs as “critical dose medicinal products” that is drugs which have narrow therapeutic range. It may be that the range we currently use as our “gold standard” does not allow us to mimic conditions under which evolution of mutants to become resistant is best represented.

The concept of the mutant prevention concentration (MPC) as introduced by Drlica and Zhao (Dong et al., 1999; Zhao and Drlica, 2001) refers to the minimal concentration of antibiotic that will prevent the selection of first step resistant mutants from a large, typical bacterial inoculum. This concept underlies consideration of the “Mutant Selection Window,” which refers to the antibiotic concentration range above the MIC and below the MPC. Although some have criticized this concept as simplistic and artificial, Drlica and Zhao have validated it in an animal model and Firsov and colleagues have presented several studies that support it (Firsov et al., 2003, 2004, 2012, 2013, 2015).

In vitro dynamic models have been used for studying the effect of duration of therapy and resistance emergence and antibiotic combinations with respect to both enhanced efficacy and preventing resistance selection, moreover in vitro dynamic models could add a dimension to current antibiotic drug development in providing potential dosing ranges for clinical trials that might provide optimal antibacterial effect and minimize the selection of antibiotic-resistant mutants.

As we are aware of inoculum differences between various infected sites and organisms, we have also learned that the local environment in terms of free ions, essential proteins and even the local pH can exert marked effects on activity and resistance selection. A more

* Corresponding author.

E-mail address: glenn.tillotson@transcrip-partners.com (G.S. Tillotson).

comprehensive appreciation of this multitude of influences on pharmacology, pharmacokinetics and ultimately the association of these with antibacterial activity and resistance emergence should underpin a more relevant array of pre-clinical and animal studies to help ensure a dose is selected for Phase 2 study that is not only safe and efficacious, but also goes some way to tackling the inevitable resistance selection we face today. These studies must be undertaken against a range of clinically relevant isolates plus some laboratory selected mutants that have not yet reached clinical practice. We must learn to pressure-test the candidate drug in as many simulations before moving to clinical trials.

Thus if we have more confidence in the final chosen dose/frequency, we can move expeditiously to a single, well-designed clinical trial in Phase 3 in a specific indication which will be supported by the above studies. Such a shift should make phase 3 trials more attractive and feasible to pharmaceutical sponsors.

Providing efficacy and some safety is established, it could be feasible to move to provisional approval pending collection of more safety and tolerability data. These data would be mandated and the sponsor would establish a secure data collection method so that on-time data is available to the Agencies.

To summarize, the need for new antibiotics is essential if we are to maintain current modern medical practice. However we model our potential drugs in systems that inadequately or incompletely reflect the actual sites of infection where several factors may interact to select for resistance, reduce efficacy and potentially create an epidemiological issue as MDR pathogens spread, it is vital that we implement new PK-PD approaches to harness these factors. More proscribed use of in vitro dynamic models, Monte Carlo analyses and other pharmacodynamic and pharmacokinetic evaluations should help us gain a deeper insight into the possible ramifications of our current methods. Perhaps new candidate drugs could utilize the different local conditions to improve their efficacy or suppress resistance selection. However, the potential benefits of these “different” drugs will need to be assessed from the standpoint of the actual infection site state; otherwise we might not recognize their possible value in the fight against MDR pathogens.

Disclosure

No payment was received by either author in the writing of this manuscript. No conflicts of interest are reported by both authors.

References

- Collignon, P., Athukorala, P.C., Senanayake, S., Khan, F., 2015. Antimicrobial resistance: the major contribution of poor governance and corruption to this growing problem. *PLoS One* 10 (3), e0116746. <http://dx.doi.org/10.1371/journal.pone.0116746>. eCollection 2015 (Mar 18).
- Dong, Y., Zhao, X., Domagala, J., Drlica, K., 1999. Effect of fluoroquinolone concentration on selection of resistant mutants of *Mycobacterium bovis* BCG and *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 43 (7), 1756–1758 (Jul).
- Firsov, A.A., Vostrov, S.N., Lubenko, I.Y., Drlica, K., Portnoy, Y.A., Zinner, S.H., 2003. In vitro pharmacodynamic evaluation of the mutant selection window hypothesis using four fluoroquinolones against *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 47 (5), 1604–1613 (May).
- Firsov, A.A., Vostrov, S.N., Lubenko, I.Y., Portnoy, Y.A., Zinner, S.H., 2004. Prevention of the selection of resistant *Staphylococcus aureus* by moxifloxacin plus doxycycline in an in vitro dynamic model: an additive effect of the combination. *Int. J. Antimicrob. Agents* 23 (5), 451–456 (May).
- Firsov, A.A., Gilbert, D., Greer, K., Portnoy, Y.A., Zinner, S.H., 2012. Comparative pharmacodynamics and antimutant potentials of doripenem and imipenem with ciprofloxacin-resistant *Pseudomonas aeruginosa* in an in vitro model. *Antimicrob. Agents Chemother.* 56 (3), 1223–1228. <http://dx.doi.org/10.1128/AAC.05964-11> (Mar, Epub 2011 Dec 27).
- Firsov, A.A., Strukova, E.N., Shlykova, D.S., Portnoy, Y.A., Kozyreva, V.K., Edelstein, M.V., Dovzhenko, S.A., Kobrin, M.B., Zinner, S.H., 2013. Bacterial resistance studies using in vitro dynamic models: the predictive power of the mutant prevention and minimum inhibitory antibiotic concentrations. *Antimicrob. Agents Chemother.* 57 (10), 4956–4962. <http://dx.doi.org/10.1128/AAC.00578-13> (Oct, Epub 2013 Jul 29).
- Firsov, A.A., Golikova, M.V., Strukova, E.N., Portnoy, Y.A., Romanov, A.V., Edelstein, M.V., Zinner, S.H., 2015. In vitro resistance studies with bacteria that exhibit low mutation frequencies: prediction of “antimutant” linezolid concentrations using a mixed inoculum containing both susceptible and resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 59 (2), 1014–1019. <http://dx.doi.org/10.1128/AAC.04214-14> (Feb, Epub 2014 Dec 1).
- Frisch, A.W., Tripp, J.D., Barrett, C.D., Pidgeon, B.E., 1942. The specific polysaccharide content of pneumonic lungs. *J. Exp. Med.* 505–510.
- Tschabitscher, D., Platzer, P., Baumgärtel, C., Müllner, M., 2008. [Generic drugs: quality, efficacy, safety and interchangeability]. [Article in German]. *Wien. Klin. Wochenschr.* 120 (3–4), 63–69. <http://dx.doi.org/10.1007/s00508-008-0927-3>.
- Zhao, X., Drlica, K., 2001. Restricting the selection of antibiotic-resistant mutants: a general strategy derived from fluoroquinolone studies. *Clin. Infect. Dis.* 33 (Suppl. 3), S147–S156 (Sep 15).