Letter to the Editor

Differences between In Vitro and In Vivo Studies

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Author’s Reply

Dr. Lorian’s major argument seems to me to be that our system did not simulate conditions antibiotics meet in serious infections, since in such infections bacteria do not grow in the body fluids but grow on the surface of epithelial cells, and, in Dr. Lorian’s opinion, in our experimental system no portion of a bacterial population could grow adherent to surfaces.

My answer to this argument is that, first of all, we very clearly stated in the introduction that our system intended to simulate only three of the conditions that may influence most activities of antibiotics during treatment of serious infections. That is to say, we most certainly did not claim to simulate all the exact conditions of serious infections. This, of course, had to be so because while differences in antibiotic concentration, number of bacteria, and environment of growth between in vitro standard assays and infections are certain, the other exact conditions antibiotics encounter in infections are largely unknown. I think I can very conservatively say that it is at least not proven yet, not in ordinary or torpid chronic infections but in the serious ones (only some aspects of which we wanted to simulate), that bacteria do not grow in the body fluids. Also still to be proven is that bacteria found in blood and urine are the result of a shedding from the actual site of infection. Actually, researchers who believe that in some infections bacteria grow forming microcolonies on epithelial surfaces suggest that this is the mechanism for subclinical or torpid chronic infections. They, however, think that when infections tend to become acute, bacteria depart from the microcolonies and invade the surrounding tissue.

It is interesting that while several papers are cited to support statements concerning the role of colonization as a prerequisite for infections (which everyone could easily agree with), no papers or experimental work is quoted in support of the statement that in serious infections (since our work deals exclusively with them) bacteria found in urine or blood are the “result of recent contamination from instrumentation or due to a rupture of a tissue that is a natural barrier” and that “bacteria do not replicate in the body fluids of patients.” On the contrary, based on most controls of our experiments, it is clear that the bacterial strains we used are all capable of growing in the various body fluids employed.

Concerning other comments of Dr. Lorian’s, I would very briefly add that the opinion that in our system bacterial adherence is completely prevented by stirring is incorrect, since in standard procedures the capability of bacteria to adhere to epithelial cells is evaluated with stirring (4, 5). Concerning this point, one should also recall the well-known ability of microorganisms grown with vigorous stirring to adhere to walls (often of glass, as in our system) of fermentors (2).

LITERATURE CITED


Also incorrect is the opinion that in our system bacteria grew fast and that stirring caused oxygenation that contributed to fast growth, since it is very clear based on the controls of our experiments that bacteria generally grew very slowly.

Finally, Dr. Lorian also mentions the fact that the ultrastructure of bacteria grown on solid media (i.e., on agar plates) is similar to that of bacteria found in infections but different from that of bacteria grown in liquid media. Concerning this, I wonder what criticism this fact could raise of our work, since it is well established based on the controls of our experiments that bacteria generally grew very slowly.

We could probably take Dr. Lorian’s comments as a suggestion to set up another system in which adherence is simulated, together with drug pharmacokinetics, number of bacteria, and environment of growth. This system could be used to better approximate in vitro conditions that antibiotics are likely to encounter in some infections, such as osteomyelitis, endocarditis, etc.

LITERATURE CITED

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