Trimethoprim-sulfamethoxazole: a reappraisal

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Trimethoprim-sulfamethoxazole is a doubly remarkable agent, remarkable in its impeccable scientific background and remarkable in its clinical achievements. As evidence of its wide clinical utility it is necessary only to draw attention to the titles of the papers in this symposium. As evidence of its achievements to date there are the records of symposia in London,[1] Melbourne and other Australian cities,[2] Sardinia[3] and Boston,[4] the rapidly growing world literature and the wealth of experience added in the present meeting.

The scientific background of the mixture is almost as well known. Trimethoprim was discovered in the laboratories of the Burroughs Wellcome Company of New York by no accident. Dr. George Hitchins and his associates had been engaged on a classic piece of antimetabolite research: a detailed elucidation of folate pathways, delineation of points at which interruption might most economically be achieved, and characterization of chemical structures likely to be most efficacious in seeking and blocking those points. This systematic study was rewarded in time by the discovery of a series of powerful drugs including mercaptopurine, azathioprine and, in due course, trimethoprim.

Properties demanded of antimicrobial agents

Much other painstaking research directed towards the synthesis of potent antimicrobial agents has received little reward. The reason is not far to seek. A useful antimicrobial agent must exhibit a truly remarkable constellation of characters. It must be able to derange a function in microorganisms that is so important that the organisms cannot grow, or perhaps even survive, without it and at the same time negate any compensatory process that the organism can muster to protect so important a mechanism from interference. As if that were not enough, a therapeutically valuable agent must achieve its effect without significant toxicity to the patient, despite the fact that many of the vital processes that might be suitable targets for inhibition are common to all living cells.

Folate supply in bacteria and man

The success of trimethoprim-sulfamethoxazole (TMP-SMX) in this connection arises directly from the detailed analysis of the different ways in which man and bacteria accumulate the folate they both need to support processes as indispensable as protein and nucleic acid synthesis. As is now well known,[5] the antimicrobial effect of TMP-SMX depends on three things:

1. Bacteria cannot absorb folate from their environments and must synthesize their needs from para-aminobenzoate — a process blocked by sulfonamide. In direct contrast, man must absorb his requirement and, because he cannot utilize the bacterial synthetic pathway, is immune from sulfonamide blockade.

2. A later stage of the folate cycle in both man and bacteria involves an enzyme, dihydrofolate reductase, that is blocked by trimethoprim. The vastly greater toxicity of trimethoprim for bacteria depends on the fact that it is bound at least 10 000 times more strongly by the bacterial than by the human enzyme. Moreover, any small effect on man can be readily offset by feeding folinic acid, which is unavailable to the parasite and enters the human folate pool beyond the point of trimethoprim blockade.

3. Because sulfonamide and trimethoprim both act, one at an early, the other at a later, stage on the same essential pathway, their simultaneous effect is markedly synergic in that the presence of one greatly potentiates the antibacterial effect of the other.

Such, then, is the success story — trimethoprim of immaculate scientific pedigree, marked synergy with sulfonamide and wide clinical efficacy of the mixture. Against that secure background must be set the poser: Accepting both the elegant scientific justification of the mixture and the overwhelming evidence of its clinical value, to what extent are science and clinical success related?

Trimethoprim as sulfonamide potentiator

So powerful was the message of synergy that trimethoprim was initially seen, by some at least, as a sulfonamide saviour. Sulfonamides are cheap, very broad-spectrum agents and the prospect that their utility might be greatly extended by trimethoprim was extremely attractive. The second edition of "Antibiotic and Chemotherapy" says "the possibility arises that trimethoprim should also be given whenever sulfonamides are used".[6] Unfortunately, sulfonamides, like so many valuable agents, have had their therapeutic place massively eroded by the development of bacterial resistance. The universal nightmare that this might be the fate of all antibacterial agents before adequate substitutes become available makes especially attractive the possibility that resistance might in some way be overcome and the previous therapeutic efficacy of agents restored. Is this, then, the role of trimethoprim — to enhance the activity of sulfonamide to the point that both sensitive and resistant organisms are therapeutically accessible?

It may come as a surprise to nonmicrobiologists to learn that the answer to this question is not too simple. The difficulty is that decreased sulfonamide susceptibility in bacteria can be associated with a number of different biochemical changes. To what extent each of these metabolic gavottes simultaneously sidesteps the action of trimethoprim has not been systematically studied. Some sulfonamide-resistant organisms, including strains of *Streptococcus faecalis*, can be inhibited by sulfonamide in the presence of trimethoprim.[7] Sulfonamide-resistant strains of some other species show no such useful interaction.[8] Until the true frequency with which the different mechanisms are represented in wild strains of organisms responsible for infections commonly treated with TMP-SMX is known, it will not be possible to say categorically to what extent the prime role of trimethoprim in clinical practice is as a sulfonamide potentiator.

Activity of trimethoprim

One striking side effect of the fascination with synergy was

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the extent to which it diverted attention from the activity of trimethoprim as an antibacterial agent in its own right. Ignoring for a moment its elegant synergic mode of action and simply comparing its *in vitro* activity with that of other notable antibacterial agents, trimethoprim is an extremely potent compound in both activity and range. Indeed, it is so active against organisms responsible for many of the infections for which TMP-SMX is used that the question becomes not "What does trimethoprim do for sulfonamide?" but "What does sulfonamide do for trimethoprim?"

Sulfonamide toxicity

There are other reasons for asking the question. The most clinically compelling is that the great majority of untoward reactions to TMP-SMX have been highly reminiscent of those associated with sulfonamide.[9] Trimethoprim can certainly depress human folate metabolism but everything known of the drug's action leads to the expectation that measurable depression will occur only with high dosage or in those with already seriously depleted folate reserves. Clinical experience has confirmed these expectations by showing that, except when the drug has been given to those of gravely suspect folate status, there have been few untoward reactions unquestionably attributable to trimethoprim. While it is plainly impossible to apportion blame irrefutably between the components of a mixture, there are strong indications that the bulk of untoward reactions to TMP-SMX are due to the sulfonamide.

Pharmacokinetics

A second reason for questioning the contribution of sulfonamide to the clinical efficacy of the mixture is that the sulfonamide and trimethoprim may not reach the same place at the same time. Great trouble was taken to select a sulfonamide with absorption and excretion characteristics as close as possible to those of trimethoprim, but the overall pharmacokinetics of the two compounds nevertheless diverge significantly. For evidence of this it is necessary to look no further than the fact that the ratio of sulfonamide to trimethoprim in the preparation is 5:1 and in the plasma 20:1. Trimethoprim is very well absorbed and almost completely excreted unchanged in the urine. The discrepancy must consequently mean that the body volume penetrated by trimethoprim is about four times that reached by sulfonamide.[10] In a word, trimethoprim goes places that sulfonamide does not. If those places are the sites of infections treated with the mixture, then the contribution of sulfonamide to the efficacy of therapy must be little or nothing.

Another pharmacokinetic fact is worth a glance. Synergic inhibition of bacteria can obviously only occur at concentrations below those at which each component is separately inhibitory. If one or other agent is present in sufficient concentration to inhibit growth by itself, then its partner has nothing to contribute. A single dose of trimethoprim produces concentrations in the urine inhibitory to *Escherichia coli* for several days. The mixture is normally given twice a day and the levels of trimethoprim alone must therefore be constantly considerably in excess of those required to inhibit a sensitive infecting organism. What part can sulfonamide play in such circumstances? There may be several.

Bacteriostatic synergy in tissues

One school of thought holds that eradication of renal infection requires adequate concentrations of the drug not only in the urine but also in the plasma. The concentration of trimethoprim in the plasma is certainly not above the inhibitory level for *E. coli* for the whole of the interdose interval. We have no idea, of course (either for this or for any other antibacterial agent), what magnitude, frequency or duration of exposure to the drug is required for elimination of infection. If we suppose that further inhibition is required after the concentration of trimethoprim has fallen to subinhibitory values, then this would be provided by the simultaneous presence of low concentrations of sulfonamide.

Bactericidal synergy

Another role for sulfonamide can be seen in its possible effect on the nature of the combination's action. It has been held that eradication of renal infection requires bactericidal drugs and that the bactericidal activity of trimethoprim is significantly enhanced by the presence of sulfonamide. I, personally, am not much impressed by either of these views.

There is ample evidence that the outcome of treatment of urinary tract infection is much the same whatever agent is used, providing the organism is not resistant to it *in vitro*. There is certainly no clear distinction to be drawn between predominantly bacteriostatic and predominantly bactericidal agents in respect of their efficacy. In another common field of TMP-SMX usage, those who are convinced of the special place of bactericidal agents in combating severe infection with *Hemophilus* species in patients with gravely impaired intrinsic pulmonary defences surely cannot have seen dramatic improvement effected by chloramphenicol when predominantly bactericidal agents have already failed.

There are unquestionably circumstances in which bactericidal agents (or bactericidal combinations) are essential, but they constitute a minute fraction of infections requiring treatment. I consequently find it hard to see any great therapeutic moment in the issue whether or not TMP-SMX always or often exhibits greater bactericidal activity than trimethoprim alone.

Control of resistance

So far, all the reasons offered for adding sulfonamide to the treatment of infections with trimethoprim have rested on bacteriostatic or bactericidal synergy. There is another reason. Organisms can produce mutants resistant to trimethoprim and some strains appear to do so relatively easily. Mutation to sulfonamide resistance is separate from that to trimethoprim and, because of the rarity of double mutation, we have every reason to expect that simultaneous treatment with the two agents will prevent the emergence of mutants resistant to either. This protective effect naturally requires that the organism be not already resistant to one of the agents and that resistance to both cannot develop simultaneously.

Confidence that these two requirements can be met in practice must be more than a little hesitant. Sulfonamide resistance is widespread in many of the species responsible for infections commonly treated with TMP-SMX, and trimethoprim resistance can be R-factor-borne, so that resistance to both components of the mixture can be simultaneously acquired.

Trimethoprim alone?

In the present state of uncertainty it is necessary finally to ask: Does all this doubt: doubt about sulfonamide protection against the emergence of trimethoprim resistance; doubt about sulfonamide toxicity; doubt about pharmacokinetic identity and doubt about the contribution of sulfonamide to the clinical efficacy of the mixture mean that we should now press for the use of trimethoprim alone? I think not, precisely because of the doubt. In such a state of uncertainty a new decision would be premature. Arguments for the use of the mixture rested on a very firm scientific basis. Arguments for its dissociation must be at least as secure. They will require supporting evidence of two kinds: evidence that the therapeutic efficacy of trimethoprim alone equals that of the mixture; and evidence that sulfonamide resistance in commonly treated species is of such a nature, magnitude and prevalence as to negate the bacteriologic arguments for the fixed addition of sulfonamide.

Some will say that such evidence already exists. I would caution against its acceptance as adequate. Statistically accept-

able evidence of superior therapeutic performance over so potent an antibacterial agent as trimethoprim demands trials of huge proportions or selection of "difficult" infections. Acute urinary tract infection, which responds readily to a great variety of agents, does not seem likely to reveal economically the mixture's superiority or lack of it. On the other hand, urinary tract infection that has already failed to respond to other treatment may do so. Enteric fever (bearing in mind the intracellular location of the parasite and the possible differential access of trimethoprim and sulfonamide to it) might well repay a comparative therapeutic study. Other appropriate test infections will come readily to mind, but they must be chosen with the unanswered questions clearly in view.

As far as the problem of sulfonamide resistance is concerned, much more extensive laboratory study is required to unravel its differential nature in relation to trimethoprim interaction and to determine the relative geographic prevalence of strains in which a useful degree of interaction can, or cannot, be obtained.

In the meantime I hold to what I have said before: "It seems that the 'fail safe' decision is to continue to prescribe the combination rather than resort at this stage to trimethoprim alone".[11]

A final aside

Fixed ratio antibacterial combinations (of which TMP-SMX is a prime example) have, as a class, been widely and justifiably castigated and banished. Many were therefore delighted to see in the acceptance of TMP-SMX in many parts of the world clear evidence that scientific appraisal of the compound in its own right had prevailed over possible doctrinaire decisions to ditch the whole class of mixtures to which it belongs.

Should it prove — and it is a long way from being proved at the moment — that the contribution of sulfonamide to the clinical utility of the mixture is substantially less than was anticipated from its scientific heritage, the decision could be taken to unscramble the mixture. It would be most unfortunate if that decision were to provoke an "I told you so: all fixed combinations are garbage" reaction that would greatly impede the proper evaluation and appropriate therapeutic use of any other mixture of solid scientific background that might in due course emerge.

If we are very lucky, one of them might prove to be as valuable as TMP-SMX.

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Comparison of ampicillin and trimethoprim-sulfamethoxazole in the short-term treatment of urinary tract infection

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Summary: Two groups, each of 20 patients, with urinary tract infection were randomly chosen and treated according to a double-blind procedure with either ampicillin, 500 mg, or trimethoprim-sulfamethoxazole, either drug being given 4 times daily for 10 days. A number of features of the infections were studied: the occurrence of single or multiple attacks, the presence or absence of complications, whether the lower or upper urinary tract was affected, and the bacteria involved. Trimethoprim-sulfamethoxazole was found to compare favourably with ampicillin in sterilizing the urine of patients with multiple and complicated urinary tract infections during a follow-up period of 3 months.

Résumé: Nous avons traité deux groupes de 20 patients porteurs d'infection urinaire. Le premier groupe reçut un comprimé de 500 mg d'ampicilline quatre fois par jour, tandis que le deuxième groupe reçut un comprimé de triméthoprime-sulfaméthoxazole quatre fois par jour pour 10 jours. L'étude s'effectua selon une méthode à double insu. L'on divisa les atteintes infectieuses de ces malades en diverses catégories: première crise ou épisodes récidivents, infections urinaires simples ou compliquées, atteinte de l'arbre urinaire supérieur ou inférieur. L'on classifia également les infections selon l'agent bactérien isolé. Les résultats montrent que l'association triméthoprime-sulfaméthoxazole est facilement comparable à l'ampicilline. Elle paraît supérieure à l'ampicilline dans le traitement des infections aiguës simples de l'arbre urinaire inférieur, et s'avère capable de stériliser les urines de malades porteurs d'une infection urinaire récidivente ou compliquée pour une période d'au moins 3 mois.

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