Today's Treatment

Use of antibiotics

Sulphonamides, co-trimoxazole, and tetracyclines

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Sulphonamides

Sulphonamides are the oldest chemotherapeutic agents whose introduction can be recalled by today's practising doctors. Although this gave them precedence of use in various treatments, they suffer from having been introduced before many of the general principles of chemotherapy had been established. They therefore sometimes acquired an unjustifiably poor reputation created by misuse, particularly in respect of dosage (see below). Furthermore, long exposure has given ample opportunity for bacterial resistance to develop. The availability of many sulphonamide derivatives with closely similar generic names has caused confusion, sometimes leading to additional therapeutic problems. Details of sulphonamides, including pharmacological properties and dosages available in Britain are given in the table; sulphonamides for topical use or specialised uses (salazopyrin, sulphapyridine) or non-absorbed derivatives for oral use are not included.

Sulphonamides all act by inhibiting an early stage of bacterial folate synthesis. Although it is usually considered that all derivatives are more or less of equal potency, perhaps because of universal cross-resistance, there are differences in activity that might be usefully exploited in conditions when effective drug concentrations may be marginal. For example, sulphadiazine, the derivative usually favoured for treating meningococcal infection and carriage in North America, is about eight times more active against *Neisseria meningitidis* than sulphadimidine, which is usually preferred in Britain. Against the pneumococcus they are about equipotent. Sulphamethoxazole, the sulphonamide component of co-trimoxazole, has four to eight times greater activity against *Escherichia coli* than sulphadimidine. After the introduction of sulphonamides, acquired bacterial resistance appeared quickly in the gonococcus but has increased more slowly in other species. Problems of resistance will be considered below along with treatment by sulphonamides. Accuracy of sensitivity testing remains a difficulty with sulphonamides, the reporting of sensitive strains as resistant being a common fault. In conditions where the outcome of treatment is not immediately critical, such as urinary infections, it is better to check for successful eradication.

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DIFFERENCES BETWEEN SULPHONAMIDE DERIVATIVES

The major differences between the sulphonamide derivatives are in their pharmacological properties and hence dosage schedules. Sulphonamides intended for systemic treatment given by mouth are all well absorbed but are eliminated from the body at very different rates, giving blood concentration half lives varying between two-and-a-half and 150 hours. The major final route of excretion is in the urine, but renal elimination depends on a combination of glomerular filtration and tubular reabsorption and secretion. Glomerular filtration is restricted by high protein binding but persistence in the body correlates poorly with this property (see table), and the rate of metabolism

Details of sulphonamides available in Britain

Generic name	Proprietary name(s)	Half-life (h)	Protein binding (%)	Free drug plasma (%)	Dosage interval (h)	Dose size‡ (g)	Comments	Derivative
Sulphacarbamide	Uromide	2·4	5	95	8	1		Short-acting
Sulphamethizole	Urolucosil	2·5	85	15	5	0·2		
Sulphathiazole	* ; also Thiazamide	4	77	23	6	0·37		
Sulphafurazole	Gantrisin	6	90	10	6	1		
Sulphadimidine	Sulphamezathine	7	79	21	6	1		
Sulphaphenazole	Orisulf	10	99	1	12	0·5		Medium-acting
Sulphamethoxazole	Gantanol†	11	68	32	12	0·8		
Sulphadiazine	*	16	45	55	12	0·4	Used alone	
					6	0·37	As component of triple sulpha§	
Sulphamerazine	*	24	75	25	6	0·26	Not used alone	
Sulphadimethoxine	Madribon	35	99	1	24	1		Long-acting
Sulphamethoxydiazine	Durenate	37	89	11	24	0·5		
Sulphamethoxypyridazine	Lederkyn, Midicel	40	92	8	24	0·5		
Sulfametopyrazine	Kelfizine	65	77	23	7 days	2		Ultra long-acting
Sulfadoxine	Fanasil	150	95	5	7 days	2	Used for malaria	

*Component of triple-sulpha combination (dosage given for individual components of Sulphatriad, one variety of combined tablets).
†Sulphonamide component of co-trimoxazole.
‡Typical dose for moderate infections in adults.
§This may be too frequent, as optimal recommended daily dose of sulphadiazine alone is 800 mg.[2]

is of at least equal importance, since unmetabolised drug retains its lipid solubility and may then undergo extensive tubular reabsorption. Metabolism increases the polarity of the drug molecules encouraging renal elimination. Unfortunately misconceptions about sulphonamide pharmacology are still perpetuated in British publications, such as the 1976-7 *British National Formulary* (BNF), where the statement "It is doubtful whether the long-acting sulphonamides, which are highly bound to serum proteins and therefore slowly excreted from the body, have any significant advantage over the short-acting agents" is far enough from accuracy as to be positively misleading. Sulfametopyrazine, an ultra long-acting derivative, is less protein bound than some short-acting sulphonamides.

It is nevertheless true that only free (non-protein-bound) drug diffuses into uninflamed tissues and fluids, such as cerebrospinal fluid and nasopharyngeal secretions. Disease may affect pharmacology by reducing the plasma albumin concentration and thus protein binding, or by reducing renal function and delaying excretion. Dosage may then need modification. The recommended dosages of some derivatives, especially sulphadiazine, are patently too large,[1] which may have accounted for problems from toxicity. We have been slow to learn from careful pharmacological evaluations and their resultant dosages published abroad.[2]

CLINICAL INDICATIONS FOR SULPHONAMIDES

There are only a few clinical indications for sulphonamides as first-line therapeutic agents. A sulphonamide alone is a reasonable choice for simple symptomatic and asymptomatic urinary infections in patients at home. Resistance to sulphonamide in the commonest urinary pathogens remains reasonably low at about 20%, although it may be more in some geographical areas. Sulphonamides are usually cheap, and used in sensible doses side effects are few. When adverse effects occur they are usually mild and not as discommoding to ambulant patients as the gastrointestinal disturbances caused by some penicillins or by tetracyclines. We have found that the dosage for sulphadimidine given in the *BNF* is far too large, causing frequent side effects. A dose of 500 mg every six hours of this and other short-acting derivatives should be adequate treatment for simple urinary infections. Although it would be reasonable to favour sulphonamides rapidly and completely excreted in the urine (that is, short-acting derivatives) for treating urinary infections, the high frequency of dosage may lead to poor patient compliance. Twice-daily, daily, and weekly prescribed derivatives have all been used successfully.

Various sulphonamides are satisfactory treatment for bacteriuria in pregnancy. As with other antibacterial agents it is important to ensure eradication of bacteriuria in pregnancy by urine culture one and five weeks after finishing the short (one-week) course of treatment. Sulphonamides should be avoided in the last two weeks of pregnancy, since placentally transferred drug may displace bilirubin from albumin and thus has the theoretical risk of causing kernicterus in the new-born, although this has been reported only with the most highly protein-bound derivatives.

A sulphonamide alone is not usually indicated in hospital urinary infections because of a higher incidence of resistance and of underlying urinary tract complications. Long-term low-dose treatment has sometimes been used to prevent recurrent urinary infection, but breakthrough infections may occur, presumably because sulphonamides tend to promote resistance in the source of infection, the bowel flora.

In meningococcal infections a parenteral sulphonamide is still used to support penicillins and to eradicate meningococci from the nasopharynx, which penicillins do not, because of poor penetration into the nasopharyngeal secretions in the absence of inflammation, despite in-vitro sensitivity. Oral sulphonamides for one week are used to treat meningococcal carriers. Resistance of *N meningitidis* to sulphonamide has increased in Britain to an extent where sensitivity cannot be assumed, and the results of testing may indicate that treatment for carriage with minocycline or rifampicin is necessary.

We do not consider non-absorbable sulphonamides useful for treating most symptomatic intestinal infections occurring in Britain, and neither are they effective in preparing the bowel for surgery. Their use as topical agents should be avoided as this may encourage sensitisation to their systemic use.

ADVERSE EFFECTS

The commonest adverse effects of sulphonamides are mild headaches and dizziness, and rashes. Rashes are usually self-limiting, and although it is both traditional and probably wise to stop treatment, the rashes we have seen in patients receiving the ultra-long-acting derivative sulfametopyrazine have not been more frequent, prolonged, or severe than those from short-acting agents.[3] In this study the incidence of rash reported by patients was 1·2%. The Stevens-Johnson syndrome, a serious and rare complication, is reputed to occur more frequently with the longer-acting agents, but many cases have been reported from hot climates where sunlight or dehydration may have played a part. Overdosage resulting from a misunderstanding of the small dose required cannot be excluded in all cases. Those reported in North America[4] were based on an unknown number of treatments, and other authors have questioned the association.[5] There was no increased association with the use of over 1 million weekly doses of sulfametopyrazine (manufacturer's data). Sulphonamides can cause kernicterus by displacing bilirubin from albumin binding and should therefore be avoided in neonates.

Other rare adverse effects are blood dyscrasias, and haemolytic anaemia in patients with G-6-PD deficiency. Crystalluria is a slight risk with sulphadiazine, but this is further reduced by maintaining a good urine flow or by using a triple sulpha preparation (sulphadiazine, sulphamerazine, and sulphathiazole).

Co-trimoxazole

Co-trimoxazole (Bactrim, Septrin) is a mixture of trimethoprim and sulphamethoxazole in a ratio of 1 : 5. The oral preparation of co-trimoxazole has been available for nearly ten years and has established a reputation as a valuable agent for treating infections of the urinary and lower respiratory tracts. Despite extensive use, some aspects of treatment with co-trimoxazole currently merit re-examination. They are the problems of resistance, the use of trimethoprim alone, and dosage.

MODE OF ACTION, AND RESISTANCE

Trimethoprim with a sulphonamide is a mixture showing bacteristatic synergy against a wide variety of bacteria, the basis of which is thought to be a sequential blockage of the folate synthesis and utilisation pathway. In antagonist-free media bactericidal action can be demonstrated, but this is slow or absent in body fluids, such as urine. It has been suggested that the combined use of the two agents might prevent resistance emerging. Thus co-trimoxazole should perhaps be used only when the infecting bacteria are sensitive to both components. This is not practicable, however, because of the difficulties of determining accurately the sensitivity to sulphonamides, and because treatment usually starts before the test results are known. Furthermore, some strains of the urinary pathogens concerned have been resistant to sulphonamides since before the introduction of co-trimoxazole, and this has not led to an appreciable emergence of trimethoprim resistance. In a survey of urinary pathogens in 1977 at four centres in Birmingham, Bristol, Dublin, and London only 3% of 788 strains of *E coli* from urinary infections in outpatients were resistant to trimetho-

prim.[6] Thus combined treatment does not seem to be rationalised at the moment by prevention of resistance to trimethoprim, which in turn seems so far to remain at a low level, although it might be argued that but for combined use the situation would now be worse. Similarly, only two of 952 strains of *Haemophilus influenzae* collected from all over Britain were resistant to trimethoprim, despite 7·6% of strains being resistant to sulphonamide.[7]

PHARMACOLOGY AND DOSAGE

Both trimethoprim and sulphamethoxazole are well absorbed after oral administration of co-trimoxazole to give blood concentrations in a ratio of 1 : 20, which is for optimal synergistic activity against many bacteria. For treating infections caused by some bacteria (for example, gonococci) or infections in certain sites, different ratios would be desirable, but this is impracticable for prescribing. Trimethoprim and sulphamethoxazole both diffuse well from the blood into body tissues and fluids, although not necessarily at the same concentrations as in the blood. Their plasma half lives are similar, allowing adequate dosing at the same intervals. Because these half lives are long (about ten hours) compared with those of many antimicrobial drugs, the recommended dosage, which does not use a loading dose, takes 72 hours to achieve the maximal blood concentrations of both drugs. These are about twice as high as after the initial dose in patients with normal renal function. This slow build-up could be obviated by using an initial double dose. The slow attainment of satisfactory blood concentrations is not important in urinary infections but is undesirable in tissue infections, such as those of the respiratory tract. For treating uncomplicated urinary infections we feel that a loading dose followed by half the currently recommended dose—that is, trimethoprim 80 mg and sulphamethoxazole 400 mg 12-hourly —is adequate treatment. A lower dosage could in theory result in fewer adverse effects.

Blood concentrations of both components are increased and prolonged by poor renal function, and doses require modification.[8] The excretion of trimethoprim is less affected and hence the ratio of blood concentrations can alter. The use of the full recommended dosage in the elderly, who often have diminished renal function, could lead to excessively high blood concentrations, which might in turn account in part for the higher incidence of adverse haematological reaction in this group of patients.

INDICATIONS FOR USING CO-TRIMOXAZOLE

Lower respiratory and urinary tract infections remain the commonest indications for co-trimoxazole. In the former the use of a potentially synergistic combination is justified because drug concentrations in the sputum may be lower than in the blood. In the urine, however, high concentrations far outweigh any potential benefit from synergism, and some authorities have questioned whether trimethoprim alone would not be equally satisfactory treatment.[9] In-vitro experiments have failed to show synergy when urine was used to grow bacteria instead of antagonist-free culture media.[10] We are not aware of any reliable treatment study showing the superiority of co-trimoxazole over trimethoprim in urinary infections. The latter has been successfully used in Finland for some time. This point is far from academic, since the sulphonamide component causes at least as many adverse reactions as trimethoprim.

It could also be questioned whether sulphamethoxazole is the best sulphonamide to combine with trimethoprim for treating urinary infections, for while it is one of the most active, it is extensively metabolised and less than half the dose is in active form in the urine. Sulphadiazine has similar high activity and is much less metabolised. Trimethoprim alone and in combination with other sulphonamides for use at both the usual and lower dosages may well appear in Britain in the next few years. This will have the advantage of offering an informed prescriber the choice of the most appropriate agent.

Other recognised uses for co-trimoxazole are the treatment of gonorrhoea, brucellosis, enteric fevers, some types of endocarditis, coliform meningitis, pneumocystis pneumonitis and febrile episodes in patients with leucopenia. For the more serious infections the parenteral preparation should be used initially.

ADVERSE EFFECTS

Adverse effects from co-trimoxazole include all those attributable to sulphonamides plus induction of folate deficiency by trimethoprim. Interference with folate metabolism is more likely in patients with pre-existing folate deficiency, when prolonged courses are given, and perhaps when excessively high drug concentrations are achieved. Folinic acid can be administered to combat haematological changes. Current evidence suggests that creatinine clearance is diminished by co-trimoxazole, probably by the trimethoprim component.[11] The clinical importance of this finding needs elucidation.

Tetracyclines

The tetracyclines have been available since 1948, but their use has been eclipsed more recently by other antibacterial drugs. As a group they have a wide spectrum of activity ranging from rickettsiae and mycoplasmas to most bacteria. Two notable exceptions are *Proteus* spp and *Pseudomonas aeruginosa*, and strains occur with acquired resistance in isolates of sensitive species. Their broad spectrum makes tetracyclines rather indiscriminate weapons and their use should be avoided when an antibiotic of narrow spectrum could be used. They remain antibiotics of at least equal first choice in (*a*) acute exacerbations of chronic bronchitis, (*b*) non-specific urethritis, (*c*) pulmonary infections with *Mycoplasma pneumoniae*, *Coxiella burnetii* (Q fever), or psittacosis, (*d*) pustular acne, (*e*) brucellosis, (*f*) lymphogranuloma venereum, (*g*) trachoma and inclusion conjunctivitis, and (*h*) rickettsial infections, especially typhus. Tetracyclines might also be considered for treating syphilis, actinomycosis, or anthrax in penicillin-allergic patients. Because of unpredictable sensitivity tetracyclines are unlikely to be first-line drugs in infections arising in hospital patients, particularly those associated with surgery. Many strains of *Streptococcus pyogenes* are resistant, and therefore tetracyclines should not be used for treating sore throats, or for the soft-tissue infections arising in domiciliary practice that are usually caused by the streptococcus or by *Staphylococcus aureus*, both of which will almost certainly be sensitive to a penicillinase-stable penicillin (for instance, flucloxacillin). Because of their lack of bactericidal activity tetracyclines should not be used when "cidal" activity is essential for successful treatment. Such instances are local defects in natural body defences (infective endocarditis or the presence of exogenous materials) and general defects (severe leucopenia). There is some resistance to tetracyclines among both *Streptococcus pneumoniae* and *H influenzae*,[12] the bacteria most commonly associated with exacerbations of chronic bronchitis and other lower respiratory infections. The choice of tetracycline for these infections must therefore depend on the local prevalence of resistance, the clinical severity of the infection, and a willingness to change treatment if there is no response. Microbiological investigation of the sputum may help.

CHOICE OF DERIVATIVE

The microbiological spectrum of all tetracyclines is with minor differences the same. There is cross-resistance between tetracyclines except minocycline, which has useful activity

against tetracycline-resistant staphylococci and possibly *H influenzae*. The choice of derivative rests on relative pharmacology, toxicity, cost, and sometimes on the condition of the patient. The preparations of tetracyclines from which to choose may be arbitrarily divided into five groups:

(1) The original compounds, tetracycline and oxytetracycline, which remain widely used despite their irregular intestinal absorption. They are the cheapest preparations.

(2) The older derivatives, methacycline, lymecycline, demeclocycline, and clomocycline, for which improved absorption resulting in higher blood concentrations and other advantages are claimed. This may allow smaller doses to be given to produce equivalent blood concentrations, but whether this results in fewer side effects is unproved. They are more expensive than group (1).

(3) Formulations with antifungal drugs or with chymotrypsin. Undoubtedly concomitant antifungal drugs do prevent the increase in the number of candida in the gut that occurs often in tetracycline treatment,[13] but there is little demonstrable clinical advantage. Their use might be justified in patients with special susceptibility to candidiasis or with very prolonged treatment.[14] Claims that oral chymotrypsin improves the tissue penetration in man of tetracycline are unsubstantiated, although intestinal absorption may be improved.[15] The preparation is expensive.

(4) Intravenous formulations (including that specifically for this route, rolitetracycline nitrate) should be used only for the rare instances when tetracyclines are the sole drugs of first choice in life-threatening infection.

(5) The most recent derivatives doxycycline and minocycline are characterised by good absorption unaffected by food and by a long plasma half-life. Both can therefore be given in smaller doses than the older tetracyclines and will have fewer gastrointestinal side effects, making them preferable for patients prone to diarrhoea. Even in their smaller dosage doxycycline and minocycline are more expensive than other tetracyclines.

DOXYCYCLINE AND MINOCYCLINE

Doxycycline is probably the only tetracycline that can be given in safety in renal failure,[16] making it the safest derivative for use in elderly ill patients. It penetrates well into tissues and the exudates that occur in sinusitis and middle ear infections.

Minocycline has a higher activity than other tetracyclines, being active against most tetracycline-resistant strains of *Staph aureus*, although minocycline should be prescribed only when narrow-spectrum antistaphylococcal drugs cannot be used. Activity against tetracycline-resistant strains of *H influenzae* and *Strep pneumoniae* is high enough to suggest that treatment of respiratory infections with normal doses of minocycline might be successful,[17] although more evidence is needed. Minocycline gives results as satisfactory as those with larger doses of other tetracyclines or other antibiotics in urinary tract infection, respiratory infection, gonorrhoea, and non-specific urethritis. Sulphonamide-resistant meningococci have been eradicated from carriers. A disturbing side effect has been a variable incidence of vertigo,[15] more common in girls and women, which ceases after stopping the drug. For this reason minocycline should be used with caution in some ambulant patients, for instance if they drive vehicles or work with machinery.

ADVERSE EFFECTS OF TETRACYCLINES

Diarrhoea is the most common of the unwanted effects of tetracyclines. Patients prone to this condition should perhaps be given one of the better-absorbed derivatives if a tetracycline is indicated. Photosensitivity may occur, especially with demeclocycline. Tetracyclines given during tooth development (that is, to the mother during pregnancy, or in the first few years of life) may cause discoloration of teeth. With the exception of doxycycline and possibly minocycline, tetracycline can cause a deterioration in already defective renal function. They should therefore be used with caution in elderly patients. Formation of complexes with antacids and iron-containing medicines occurs to a variable degree with all tetracyclines, resulting in poor absorption, and antacids should therefore not be given at the same times as a tetracycline, or another type of antibiotic should be used.

References

1 Garrod, L P, Lambert, H P, and O'Grady, F, *Antibiotic and Chemotherapy*, p 27. Edinburgh, Churchill Livingstone, 1973.'
2 Otten, H, Plempel, M, Siegenthaler, W, *Antikiotika-Fibel*, p 130. Stuttgart, Thieme, 1975.
3 Reeves, D S, *Journal of Antimicrobial Chemotherapy*, 1975, **1**, 171.
4 Carroll, O M, Bryan, P A, and Robinson, R J, *Journal of the American Medical Association*, 1966, **195**, 691.
5 Bianchine, J R, *et al*, *American Journal of Medicine*, 1968, **44**, 390.
6 Emmerson, A M, *et al*, unpublished data.
7 Howard, A, J, *et al*. In press.
8 Tasker, P R W, *et al*, *Lancet*, 1975, **1**, 1216.
9 Brumfitt, W, *et al*, *Urinary Tract Infection*, ed W Brumfitt and A W, Asscher, p 229. London, Oxford University Press, 1973.
10 Anderson, J D, *et al*, *Journal of Clinical Pathology*, 1974, **27**, 619.
11 Shouval, D, Ligumsky, M, and Benjshay, D, *Lancet*, 1978, **1**, 244.
12 Williams, J D, and Andrews, J, *British Medical Journal*, 1974, **1**, 134.
13 Middleton, R S W, *British Journal of Clinical Practice*, 1967, **21**, 179.
14 Robinson, M M, *Antibiotics Annual, 1957-8*, p 451.
15 Seneca, H, and Peer, P, *Antimicrobial Agents and Chemotherapy*, 1963, **3**, 657.
16 Jacobs, C, and Legrain, M, *Gazette Médicale de France*, 1971, **78**, 3981.
17 Wood, M J, *et al*, *Journal of Antimicrobial Chemotherapy*, 1975, **1**, 323.
18 Williams, D N, Laughlin, L W, and Lee, Y-H, *Lancet*, 1974, **2**, 744.

How should self-examination of the breast be carried out and how often should it be done?

Regular self-examination of the breasts is probably best begun in the late teens or early 20s. A woman will thus learn the normal consistency of her breasts before there is anxiety about the possible presence of cancer. Monthly examination should be carried out through life, and the best time is immediately after the end of each period when the breasts are most quiescent and least "lumpy." At the menopause the time is changed to, say, the first day of each calendar month. The breasts should first be examined in front of a well-lit mirror. The anterior aspects of the breasts and the nipples are compared with the arms at the side. There are slight variations between the size of the breasts and the nipple shape in some otherwise normal women. It is change that is important—such as a nipple becoming inverted after being everted, which may be significant. The woman should then raise her arms slowly and evenly above her head while watching for a change in contour of one breast, a slight puckering of the skin, or the failure of the breast tissue to slip easily over the underlying structures.

The breast tissue itself should next be examined. The woman should lie on a bed with a pillow alternately under each shoulder, and use the flat of the opposite hand to palpate each breast. Each quadrant should be examined from the periphery towards the nipple along, say, three radii each time. To detect lesions at an earlier stage than this, a woman may learn to palpate the breasts with the tips of all her four fingers touching in a line, with the palm "cupped." She will feel the tissues more easily and efficiently if she soaps the skin, and this examination may be carried out in the bath. It may be best to use the left hand to palpate the right halves of each breast, and vice versa. The soap acts as an interface and allows the subcutaneous tissues immediately under the skin to be felt with very light pressure (as one would use in stroking the surface of material to feel the grain), and the deeper structures within the breasts can be felt by using more pressure along the radii of each quadrant as in the flat-of-the-hand method. The finger method may show the presence of smaller lesions and also areas of localised dysplasia, which may warrant further investigation.