

General Practice

Another Look at Erythromycin

J. L. STRAUGHAN

SUMMARY

The erythromycins are broadly reviewed from a clinical viewpoint. The antimicrobial spectrum, clinical indications, pharmacokinetics and toxicity are dealt with. The usefulness of erythromycin for respiratory tract infections is stressed. New evidence to support bactericidal activity of this antibiotic is noted. There seems little reason to use the potentially hepatotoxic estolate form of erythromycin. The safety of the other forms of this antibiotic available in this country is emphasized.

S. Afr. med. J., **53**, 527 (1978).

In 1952 erythromycin was discovered among the metabolic products of a strain of *Streptomyces erythreus* Waksman, from the fungal growth in a soil sample from the Philippines.

Hosts of new and allegedly new antibiotics have made their appearance since 1952, and these newcomers tend to displace interest in, and familiarity with, the benefits of some of the older agents still available. In their latest edition of *Antibiotic and Chemotherapy*, Garrod *et al.*¹ state that 'Leaving aside the special problem of the hepatotoxicity of the estolate, there is no doubt that erythromycin is one of the most innocuous antibiotics in current use'. As this article hopes to show, it is also one of the most useful antibiotics available, especially in general practice.

WHAT IS ERYTHROMYCIN?

Erythromycin is classified as a macrolide antibiotic. The word 'macrolide' indicates that it has a macrocyclic lactone ring in its chemical structure. It is chiefly an antibacterial agent but is active against other micro-organisms as well.

Marked instability of the basic erythromycin molecule in an acid environment has led pharmaceutical researchers to produce derivatives of the parent drug which are more acid-resistant and better absorbed. Thus, a variety of forms for oral use are on the market, which make use of relatively acid-resistant derivatives or acid-resistant formulations, or both.

WHAT IS THE MECHANISM OF ACTION OF ERYTHROMYCIN?

Erythromycin inhibits protein synthesis within the cells of micro-organisms because it binds with the 50S ribosomal

subunit of the organisms and arrests peptide bond formation.²⁻⁴ Thus its primary action is intracellular, and therefore effective against most of the clinically important strains of *Mycoplasma*, and selectively toxic for micro-organisms because there is no 50S subunit to the ribosomes of the human host.

IS ERYTHROMYCIN BACTERIOSTATIC OR BACTERICIDAL?

The answer to this question is 'both'. Depending on the organism in question and the concentration of the antibiotic that can be attained in its environments, erythromycin can behave bactericidally or bacteriostatically, or indeed be quite ineffective.⁵ The same can be said for the antibiotic penicillin. The terms bactericidal and bacteriostatic are always relative.^{6,7} At the low dosages recommended for both penicillin V and for erythromycin in the treatment of rheumatic fever, the antibiotics produce levels that are lethal (cidal) to the highly susceptible group A β -haemolytic *Streptococcus* but scarcely affect other organisms at all — which accounts for the innocuous nature of the prophylaxis.

Elegant studies reported at the 1977 International Congress on Chemotherapy showed that 500 mg of erythromycin stearate administered 3 times a day to adults suffering from acute upper respiratory infections was bactericidal *in vivo* to group A β -haemolytic streptococci, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*.⁸

WHAT IS THE ANTIMICROBIAL SPECTRUM OF ERYTHROMYCIN?

Erythromycin is very active against many Gram-positive cocci, in particular *Staphylococcus pyogenes*, *Diplococcus pneumoniae*, *Streptococcus viridans* and *S. pyogenes*. The penicillinase-producing *Staphylococcus* strains are also susceptible to erythromycin.

Of the Gram-positive bacilli, the following are susceptible to the action of erythromycin: *Corynebacterium diphtheriae*, *C. minutissimum*, *Bacillus anthracis*, *Clostridium tetani*, *Cl. perfringens (welchii)*, and *Listeria monocytogenes*. Of the Gram-negative bacteria, *Neisseria meningitidis*, *N. gonorrhoeae*, *Haemophilus influenzae* and *Bordetella pertussis* are susceptible. Many *Brucella* spp. and *Yersinia* spp. are also susceptible, as is the *Fusobacterium fusiforme* of Vincent's angina. It has even been reported that most strains of *Escherichia coli* and *Klebsiella* are inhibited in the urinary tract, provided the urine is rendered alkaline by the use of systemic alkalinizers such as potassium citrate/sodium citrate, etc.⁹ More studies in this regard would seem to be indicated.

Department of Pharmacology, University of Stellenbosch, Parowvallei, CP

J. L. STRAUGHAN, B.S.C. (PHARM.), M.B. CH.B., B.S.C. HONS

Date received: 23 January 1978.

Recent surveys show that many *Bacteroides* spp., *Treponema pallidum* and the actinomycetes are susceptible to erythromycin.³⁰ Some rickettsial organisms responsible for typhus fevers are also susceptible to this antibiotic, as is *Chlamydia*. *Mycoplasma pneumoniae* is highly susceptible to erythromycin.

FOR WHAT CONDITIONS IS ERYTHROMYCIN MOST USEFUL?

The efficacy of this antibiotic against so many Gram-positive cocci and against *H. influenzae* and *Mycoplasma pneumoniae* makes it an excellent respiratory tract antibiotic. Thus this antibiotic is recommended for streptococcal tonsillopharyngitis, and for other pharyngeal infections, for sinusitis, otitis media, laryngitis, tracheitis, and acute bronchitis, and for primary atypical pneumonia.

For persons allergic to penicillin who require an antibacterial agent with the spectrum of penicillin G or V, erythromycin is probably the drug of choice, provided that penetration across the blood-brain barrier is not required, such as in bacterial meningitis. For the treatment of rheumatic fever, erythromycin is the drug of choice after penicillin. For the treatment of soft-tissue infections, erythromycin can be very useful, especially when penicillinase-producing organisms are involved. A wide selection of penicillinase-resistant agents is available nowadays, yet for boils, styes, paronychia, impetigo, cellulitis, etc., relatively minor but everyday conditions, this antibiotic would seem to recommend itself. In the management of diphtheria, both symptomatic and asymptomatic (carrier), erythromycin is considered to be a very good choice.³¹ Prostatitis and 'nonspecific' urethritis frequently involve infection with *Chlamydia*, and the use of erythromycin for such conditions might be recommended.

Bacteroides spp., the cause of many anaerobic infections, are very susceptible to erythromycin. Erythromycin is highly effective in eradicating the organism involved in pertussis from the nasopharynx of affected persons and from carriers.³² A course of 10 days' duration is currently recommended for paediatric use,³³ although uncontrolled trials would indicate that 5 days' treatment might be just as effective.³⁴ In the treatment of primary syphilis, erythromycin is an acceptable alternative to penicillin. Uncontrolled trials indicate that erythromycin is also very useful in the treatment of acne requiring antimicrobial treatment.

WHAT IS KNOWN OF THE PHARMACOKINETICS OF ERYTHROMYCIN?

The aspect of pharmacokinetics brings to the fore some rather more problematical material. Erythromycin for oral use is available in several forms and formulations in South Africa: erythromycin base, erythromycin stearate, erythromycin ethylsuccinate, erythromycin ethylcarbonate, and erythromycin estolate.

Bio-availability

With regard to bio-availability the following points seem pertinent: The base is very unstable in an acid medium and is therefore protected from the gastric juice by applying various acid-resistant coatings to the tablet and capsule products utilizing the base. Provided that the product releases its contents satisfactorily in the small bowel, the erythromycin base will be well absorbed;^{15,36} however, wide variations in absorption rate are common when the base is administered. The stearate is relatively acid-stable and is dissociated from the base in the small intestine, and the active erythromycin is subsequently absorbed.

The ethylsuccinate and the ethylcarbonate are still more acid-stable. These forms are virtually tasteless and are therefore used in paediatric formulations, such as suspensions and sachets. These forms are well absorbed, chiefly from the small intestine, are absorbed intact and have to be hydrolyzed systemically. The hydrolysis of these two esters takes place very rapidly, so these forms of the antibiotic also give highly acceptable levels of erythromycin base. It is important to note that only the erythromycin base demonstrates antimicrobial activity.³⁷

Erythromycin estolate, which is tasteless, is well absorbed from the gut, even in the presence of food, and is acid-stable, so that good serum levels of the estolate are found.³⁸ However, a problem arises with regard to the rate and degree of hydrolysis that occurs systemically. The excellent serum levels provided by this form of erythromycin are a reflection of the total level of estolate plus base, and to date, no entirely satisfactory data are available to provide an insight into the absolute levels of the base alone formed *in vivo*.

This whole topic is still highly contentious and it seems that we should still be guided by the fact that treatment with the various salts and esters of erythromycin seems comparable in terms of efficacy, and that, excluding toxicity, there would appear to be little reason for choosing one form rather than another.

Unpublished data suggest that bio-availability differences among some products of erythromycin available in South Africa do exist;¹⁹ this should be considered as a cause for concern.

Distribution

Erythromycin penetrates all body fluids and tissues well, with the important exception of the brain and cerebrospinal fluid. The cerebrospinal fluid levels must be considered inadequate for therapeutic efficacy, especially when other agents that penetrate the blood-brain barrier more effectively are available. The levels found in fetal serum reflect from 5% to 20% of maternal serum levels, while breast milk levels reflect some 50% of the serum levels.

Concentrations of erythromycin in urine are very low; 2-5% of an oral dose finds its way out via the urine. The efficacy of this antibiotic in, for example, chlamydial urethritis,³⁹ probably indicates good tissue levels and poor urine levels.

A study reported at the 1977 International Congress on Chemotherapy indicates that erythromycin provides very good levels in the bronchi and in the bronchial secretions.²¹ The study accentuates the value of this antibiotic in respiratory infections caused by susceptible organisms. Protein binding is 70-90% at the usual therapeutic serum levels.²²

Elimination

Biliary levels of active antibiotic are several times higher than serum levels. As the urinary levels are very low, dosage schedules probably require no adjustment in persons with renal impairment.²³

The bile and faeces are the main means of excretion. The drug should probably be used with caution in persons with hepatic failure, even though hepatic biotransformation is minimal. The serum half-life of erythromycin is 1-2 hours. Peak serum levels are attained 1-4 hours after oral administration.

WHAT ADVERSE REACTIONS CAN BE EXPECTED FROM ERYTHROMYCIN?

With the exception of the estolate, erythromycin is one of the most innocuous antibacterial agents in use at present; the reactions that do occur are very seldom serious, and their incidence is very low. Gastro-intestinal side-effects (nausea, epigastric discomfort or pain, vomiting, diarrhoea) are the most likely and are seldom severe. Allergic reactions with or without pyrexia can occur with eosinophilia and skin rash. Superinfection is a risk but is generally considered to be less of a problem with the narrow-spectrum antibacterial agents than with the broad-spectrum agents.

The cholestatic jaundice that occurs when the estolate is used is the adverse reaction of concern. It has been said that the incidence of this problem in children under the age of 12 years is almost non-existent.²⁴ However, the incidence of overt jaundice in older patients has led to certain restrictions on, or withdrawal of, the estolate derivative in some countries. The problem is very rare with shorter courses of the estolate. However, if it has occurred once, its recurrence on re-exposure to the estolate seems invariable. Subsequent use of the other forms of erythromycin is without hazard.

Consistent clinical features of the syndrome are: malaise, nausea, vomiting, and varying degrees of abdominal pain, with low-grade fever and jaundice developing in about half of the individuals affected. A maculopapular rash has been reported in about 10% of patients. The condition is generally associated with an increase in serum concentrations of transaminase, alkaline phosphatase, bilirubin, and cholesterol. Eosinophilia is also found in 50% of these patients. Prospective studies have failed to demonstrate a relationship between the use of the estolate and changes in blood chemistry which might predict hepatotoxicity.²⁵⁻²⁷ Once medication is discontinued, recovery is prompt and usually occurs within a week; complete resolution is usual, but residual hepatic dysfunction has been reported.^{28,29}

The prompt recurrence of the syndrome in persons re-exposed to the estolate suggests that the cholestasis results from some type of hypersensitivity reaction, although details of the process are not known. It has been suggested that the 2'-carbon ester linkage of the propionate to the parent molecule is responsible for the toxicity.³⁰

It has, however, also been shown that substances with strong detergent-like activity are capable of damaging cells in culture, and that their detergent potency parallels their hepatotoxicity.³¹ Thus it was found that erythromycin cetyl sulphate was very hepatotoxic in humans (which led to its rapid withdrawal from the pharmaceutical market) and that the detergent potency of this form was even greater than that of the estolate.

In 1973, a report from the Australian Drug Evaluation Committee concluded that 'current data demonstrate no advantage in clinical efficacy for the estolate, but a clearly increased risk of a specific reaction leading to a significant morbidity in adults and older children.'³² This would seem to indicate the attitude that should be adopted in 1978, until more definitive data become available to show cause for a change of opinion.

IS DEVELOPMENT OF RESISTANCE A PROBLEM WITH ERYTHROMYCIN?

Many textbooks and handbooks emphasize that the development of resistance to erythromycin is a common problem. However, it seems that *de novo* resistance of bacteria normally susceptible to erythromycin is rare. Strains with such resistance do occur, but invariably in a hospital situation where no adequate antibiotic rotation schedule exists, and where the antibiotic is widely used. Under such circumstances, resistant strains are selected and get passed from one patient to another. Moreover, the opinion has been expressed that acquired resistance is virtually unknown,³³ and that in general practice, problems with resistance are highly unlikely.³⁴ The use of erythromycin would not be expected to lead to the selection of resistant *E. coli*, because *E. coli* do not possess factors resistant to erythromycin. Thus the commensal *E. coli* in the gut, the most common source of resistance factors, would not be expected to cause this problem.

This author also states that the idea that bacteria mutate to erythromycin resistance is probably erroneous, and he doubts that mutation occurs, even with prolonged use of the drug.³⁴ A recent report³⁵ based on findings in general practice indicates that the incidence of resistance to erythromycin among *Staphylococcus aureus* isolated from throat swabs over a 15-month period was zero. This was while erythromycin was being used as the treatment of first choice for upper respiratory tract infections.

WHAT OF THE PARENTERAL FORMULATIONS OF ERYTHROMYCIN?

For parenteral administration the following forms of erythromycin are available: erythromycin ethylsuccinate for intramuscular administration, and erythromycin lactobionate for intravenous use. The intramuscular injection is very painful and should definitely not be used in child-

ren. The site of injection remains very tender for a long time.

Erythromycin for intravenous administration gives rise to local thrombophlebitis if not administered well diluted. Physical incompatibilities in infusion therapy are enumerated by the manufacturers, whose recommendations should be closely followed. Recourse to parenteral intravenous administration is warranted in exceptional circumstances.

WHAT DOSAGES OF ERYTHROMYCIN ARE RECOMMENDED?

The usual adult dose is 1-4 g per day. The prolonged effective tissue levels make a twice-a-day regimen quite feasible. However, individual doses in excess of 500 mg should be divided, so that a maximum of 500 mg is ingested as a single dose to minimize gastro-intestinal intolerance. For children the usual oral dosage is 25-50 mg/kg/d, divided so as to be administered 2 or 4 times a day. For the management of rheumatic fever, the dosage is 250-500 mg/d for children of a mass in excess of 35 kg, and for those of lesser mass 125-250 mg/d. For adults 250-500 mg/d is recommended.

Uncontrolled trials suggest that for acne a maintenance dose of 250 mg/d is often adequate. The estolate should be avoided for long-term treatment. As an alternative to penicillin in the treatment of primary syphilis, 2-4 g/d should be administered for 10-15 days.

Because antibiotics should never be prescribed without good cause, when they are prescribed they should be administered in such a way as to ensure maximal efficacy.

Thus in order to ensure optimal bio-availability, it is recommended that all forms of erythromycin be administered in accordance with the package insert recommendations.

CONCLUSION

With the exception of the estolate derivative, erythromycin is a very safe and non-toxic antibiotic that recommends itself for more widespread use, especially in

general practice. It is especially recommended for use as a respiratory tract antibiotic. In practice, there would seem to be little reason for making use of the potentially hepatotoxic estolate. The parenteral forms should seldom be necessary in general practice and the intramuscular form is particularly painful.

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