Dose-response relationships in clinical pharmacology.
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DOSE-RESPONSE RELATIONSHIPS IN ANTIMICROBIAL THERAPY

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Antibiotics have no (or only minimal) effect on human cells and tissues - their action is directed specifically against micro-organisms. This differentiates them from all other medications. Dose/response relationships are therefore difficult to quantify with antibiotics and remarkably little scientific information is available on this subject. The definition of an antibiotic as "A drug given in a dose of 500mg every six hours" indicates the empirical nature of antimicrobial chemotherapy! With many antibiotics such a dosage regime will be effective and non-toxic; this is especially so with the penicillins and cephalosporins (the beta-lactam agents) which are generally safe drugs with a wide therapeutic index. A dose of 500mg fits readily into tablets and capsules and will be effective in most mild to moderate infections provided the causative organism is sensitive. However, higher doses may be required for serious infections or less sensitive bacteria.

Much more attention has been paid to the sensitivity of bacteria to antibiotics than to their *in vivo* effects which are more difficult to measure and predict. Thus, the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic for a particular organism - which are relatively simple to measure - have become the most important determinants of antibiotic dosage.

In certain infections in which cure is relatively simple to achieve the

TABLE 1

ASSESSMENT OF RESPONSE TO ANTIMICROBIAL THERAPY

RELIEF OF SYMPTOMS	
e.g.	Headache
	Cough
	Dysuria
RESOLUTION OF SIGNS	
	Fever
	Swelling
	Tenderness
ERADICATION OF ORGANISM	
from	Blood
	Urine
	Sputum
RADIOLOGICAL IMPROVEMENT	
	X-ray
	Scan

dose of an antibiotic is not particularly important. An example is uncomplicated urinary tract infection; provided the chosen antibiotic is excreted in the urine and the infecting organism is sensitive to that agent, then eradication of the infection will be achieved with a modest dose given by mouth for a short period of time. Indeed, such infections can be cured by a single dose of antibiotic. However, in deep-seated infections involving vital organs such as the heart and central nervous system, the dose of an antibiotic and the frequency of it's administration can be critical.

Assessing response to antibiotic therapy can be complex as compared with many other therapeutic substances; Table 1 lists the factors that must be taken into consideration. With other drugs response to therapy can often be measured more specifically either by physiological measurements (eg blood pressure) or by assessing relief of symptoms (eg pain).

Table 2 lists relevant factors to be considered when selecting the dose of an antibiotic for the treatment of a specific infection. The key factors are the disease process (the infection), the known or presumed causative organism, the status of the patient and the properties of the chosen antibiotic. If the patient is young (but not a neonate) with normal immune, liver and renal function and is suffering from an uncomplicated infection (eg lobar pneumonia) caused by a known organism (Streptococcus pneumoniae) of predictable sensitivity (to penicillin in the UK) then cure will be guaranteed with a modest dose (500mg) of ampicillin given by mouth every eight hours for five days. If, however, the patient has pneumococcal meningitis or is immunosuppressed it will be necessary to give large doses

TABLE 2

DOSE OF AN ANTIMICROBIAL AGENT - SOME RELEVANT FACTORS

PHARMACOLOGY OF THE DRUG
Oral/parenteral administration
Elimination half-life
Distribution in the body
Protein binding
Tissue penetration
Cell penetration (mammalian, microbial)
TOXICOLOGY OF THE DRUG
Dose related ?
Not dose related ?
MICROBIOLOGY OF THE INFECTION
Causative organism
MIC/MBC
Post-antibiotic effect
THE INFECTION
Site
Severity
Associated prosthesis
THE PATIENT
Age
Immune function
Renal/hepatic function

of benzylpenicillin (eg 1200mg) by intravenous injection every four hours.

Patients who are immunosuppressed or have prostheses in situ require special consideration with regard to dosage and frequency of administration of an antibiotic. Neutropenic patients are especially susceptible to bacterial infections which can be rapidly fatal if appropriate antibiotic therapy in effective dosage is not started as early as possible in the course of the illness. Infections associated with artificial heart valves and prosthetic joints are especially difficult to eradicate and require careful attention to antibiotic dosage and frequency of administration.

The present paper will discuss dose/response relationships in the context of certain clinical problems:-

[1] Urinary tract infection.

[2] Bacterial meningitis.

[3] Salmonella septicaemia.

[4] Aminoglycoside therapy.

URINARY TRACT INFECTION

There has been considerable debate as to the total dose of an antimicrobial agent required for the treatment of urinary tract infection. Traditional teaching recommended full dosage continued for seven to ten days. One study, however, suggested that cure could be obtained in uncomplicated urinary tract infection with a single dose of 3g of amoxycillin. More recently Blackstone[1] has reported that a single dose of only 100mg of trimethoprim was as effective as a five or seven day course, again in uncomplicated urinary tract infection. However, another study[2], also published in 1988 showed that single dose co-trimoxazole (trimethoprim

plus sulphamethoxazole) was not as effective as conventional regimes for the management of acute urinary tract infection in children. This study found a 93% initial cure rate with both single dose and multi-dose regimens. However, at follow-up relapse occurred in 20% of patients treated with a single dose compared with 8% in those given twice daily dosage for three days and 6% treated for seven days. This illustrates the importance of careful follow-up when assessing dose response relationships in the treatment of infection. In complicated urinary tract infection it is often necessary to continue treatment with full dosage for at least ten days, and if there is associated prostatitis for six weeks.

BACTERIAL MENINGITIS

Whereas it is relatively simple to conduct clinical trials of antibiotics in urinary tract infection this is not so in pyogenic meningitis. As a result information on dose/response relationships is relatively sparse. It has been traditional to prescribe large doses of penicillin (eg 2400mg) given intravenously every four hours for meningococcal and pneumococcal infections. Until recently neonatal meningitis which is commonly caused by Gram-negative bacilli such as Escherichia coli was treated with an aminoglycoside such as gentamicin. Because of the dose-related toxic effects of the aminoglycosides on the ear and kidney it was usually impossible to achieve therapeutic antibiotic concentrations in the cerebro-spinal fluid (CSF) and intra-thecal (usually intraventricular) injection of the aminoglycoside was therefore essential for cure. Even with this regimen response rates were poor and babies often died. Sande[3] has stated that CSF antibiotic concentrations to MIC of bacteria of greater than 10:1 was the most critical determining factor for success of therapy in bacterial

meningitis. These concentrations are difficult to achieve with the aminoglycosides. The extended spectrum (third generation) cephalosporins have now replaced the aminoglycosides for the treatment of neonatal meningitis. Steele and Bradsher[4] have studied ceftriaxone and have shown that this third generation cephalosporin, which is 97% protein bound but is not secreted by renal tubules, and therefore has a prolonged serum half-life, is as effective as a single daily dose in the treatment of paediatric meningitis. Table 3 shows the pharmacological results obtained by these workers which satisfy Sande's criterion. Another more recent study[5] has shown that seven days of ceftriaxone is as effective as ten days for the treatment of paediatric meningitis.

SALMONELLA SEPTICAEMIA

Two recent patients suffering from salmonella septicaemia who were recently under our care illustrate the problems of managing this infection.

[1] A young man presented with backache and fever following a holiday in North Africa. CT scan showed a lesion in the thoracic spine compatible with bone infection and a salmonella species was cultured from his blood. As the organism was resistant to most other antimicrobial agents treatment was commenced with chloramphenicol 750mg every six hours (MIC of the organism for this antibiotic was 4mcg/ml) but there was no clinical response and blood cultures remained positive. Treatment was changed to ciprofloxacin, a new quinolone antibiotic, in a dose of 200mg IV 12 hourly with relief of pain, resolution of fever and sterilization of the blood. This agent was continued for six months with healing of the osteomyelitis.

[2] An adult male suffering from acute leukaemia with neutropenia

TABLE 3

CEFTRIAXONE IN PAEDIATRIC MENINGITIS
(Steele & Bradsher, J Paediat, July 1983)

Single daily dose of 50mg/kg of ceftriaxone

Peak plasma concentrations	-	295 ± 76mcg/ml
Elimination half-life	-	5.4 ± 2.1 hrs
CSF concentration (1-6hrs)	-	6.4 mcg/ml
(after 4 doses	-	11mcg/ml)
MIC of causative bacteria	-	≤ 0.06mcg/ml

$$\frac{\text{CSF concentration}}{\text{MIC of bacteria}} = \frac{100}{1}$$

developed a salmonella septicaemia and a splenic abscess. The organism was multi-resistant and only sensitive to ceftazidime, mecillinam, imipenem and ciprofloxacin (MIC's ranging from 0.1 - 0.01mcg/ml). Treatment with the first three of these, all beta-lactam agents, alone and in combination, given in high dosage (up to 6g/day) failed to control the infection. Ciprofloxacin, however, in a dose of only 200mg 12 hourly resulted in cure of the infection and resolution of the abscess in the spleen.

These two cases illustrate several points:-

(i) Chloramphenicol failed to cure the septicaemia as the organism was relatively resistant to this antibiotic and it was probably impossible with the dosage used (the maximum safe dose) to achieve therapeutic levels of the antibiotic at the site of infection in the spine.

(ii) The beta-lactam agents, even in combination and in high dosage, did not eradicate the infection in the second patient although the infecting organism was highly sensitive to all of them. This is a well recognised fact and is probably due to the failure of beta-lactam agents to penetrate infected cells and cure intracellular infections such as those caused by salmonellae.

(iii) Ciprofloxacin, in low dosage and only given twice a day cured both patients almost certainly due to it's excellent penetration into tissues and cells including macrophages. The peak serum level of ciprofloxacin (a drug with dose-related side-effects) following a 200mg IV dose is between 2mcg/ml and 4mcg/ml compared with levels of approximately 200mcg/ml following 2g of ceftazidime which was given to the immunocompromised septicaemic patient.

AMINOGLYCOSIDE ANTIBIOTICS

The aminoglycoside group of antibiotics, streptomycin, kanamycin, gentamicin, tobramycin and amikacin are toxic both to the ear and to the kidney. The toxicity is closely associated with serum concentrations of the antibiotics and their dosage must therefore be carefully calculated and blood levels monitored during therapy. Gentamicin is widely used for the treatment of serious infections such as septicaemia and endocarditis in spite of it's toxicity as it is more rapidly bactericidal than the beta-lactam agents which are the alternative drugs for these life-threatening infections. Unlike the beta-lactams it also has a prolonged post-antibiotic effect, the phenomenum of suppression of bacterial growth after a short exposure of bacteria to antimicrobials. This effect is due to prior antimicrobial exposure and not to the action of persisting concentrations of the drug[6]. The therapeutic outcome with gentamicin is influenced by the area under the curve in the serum whereas with the beta-lactams this is not concentration dependent.

Because of these pharmacological and microbiological properties frequent dosing schedules or constant infusion of the aminoglycosides is not necessary as it is with the beta-lactam antibiotics. In experimental pseudomonas pneumonia in guinea pigs Kapusnik et al[7] found that single large doses of tobramycin were less toxic than conventional dosing and the higher drug concentrations in the blood produced more rapid bacterial killing. Wood et al[8] in a rat subcutaneous abscess model found that there was a consistent trend of greater kidney injury with more frequent dosage regimes but that a single daily dose was just as effective as 12 hourly, 8 hourly and 4 hourly regimens. Moore et al[9] in review of 236 patients with serious Gram-negative bacillary infections found a reduction in response rate from

85% to 55% once the ratio of peak serum level to MIC was less than six. This finding would support the concept of single large daily doses of aminoglycosides. Kapusnik and Sande[10] using experimental models reported that high transient peak concentrations of aminoglycosides (as obtained with single daily dosage) were better than low frequent peak serum levels for the therapy of pseudomonas pneumonia but that frequent low peak concentrations were superior for the synergistic therapy (with penicillin) of experimental endocarditis.

The clinical significance of the above studies is not entirely clear but would support single large dose aminoglycoside therapy for serious Gram-negative bacillary infection and more frequent low dose administration for streptococcal endocarditis in which gentamicin is given in combination with penicillin to provide syndergistic support. The Endocarditis Working Party of the British Society for Antimicrobial Chemotherapy[11] recommends treating streptococcal endocarditis with low dose (60 or 80mg 12 hourly) gentamicin plus penicillin. This achieves synergistic activity between the two antibiotics with only minimal risk of aminoglycoside toxicity. This risk is further minimised by shortening the course of therapy from the traditional duration of six weeks to from two to four weeks.

SUMMARY

Dose/response relationships with antibiotics can be difficult to measure. In the past more attention has been paid to the sensitivity of the infecting organism, and whether or not it has been eradicated, than to quantifying the clinical response of the patient. Most antibiotics do not have dose-related

adverse reactions unless very high doses are given (eg neurotoxicity with the beta-lactams) and the stimulus to study dose/response relationships is therefore absent. The best studies have been carried out with the aminoglycoside antibiotics which have a narrow therapeutic index. There is some evidence that whereas the dosing schedules for beta-lactam agents should maintain drug concentrations (and perhaps free concentrations, i.e. not protein bound) in excess of the MIC for the infecting organism for the entire dosing interval this is less important with the aminoglycosides which can be given by infrequent bolus administration of relatively high doses[12].

The relationship between duration of antibiotic therapy and response to treatment is also uncertain even in relatively easily studied diseases such as urinary tract infection. Each patient should probably be managed on an individual basis in order to obtain the best results. Whereas unduly short courses of therapy may be insufficient in urinary tract infection there has been a tendency to overtreat infective endocarditis.

Finally, failure of therapy may not be related to dosage but to the inability of certain antibiotics to reach the infecting organism within tissues or cells.

Agents with long serum half-lives such as ceftriaxone may allow single daily dose therapy of serious infections such as meningitis although consideration must be given to the high protein binding of such antibiotics resulting in low levels of unbound drug in the blood and at the site of infection. Wise[13] has stated that only when binding is very high, probably in excess of 90%, that unfavourable clinical effects become apparent.

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Discussion - Dose-response relationships in antimicrobial therapy

L. Lasagna

Antimicrobial chemotherapy is a tough field in which to do dose-response studies, because ethically you would be out of your mind to set up purposely to evaluate dose-responses with any but the most trivial infections. There are some controlled trials one can do comparing drugs that look about the same, to see whether there might be a little advantage of one or the other in terms of side effects or efficacy. But I wonder whether this is in an area where naturalistic and epidemiological studies really don't need to be applied more. It seems to me that one can look at hospitals and see them changing regimens for how they treat, for example, sepsis of undetermined etiology and sometimes you notice that in a given year things are looking a lot better or a lot worse than they were with the regimen used before. Of course, there may be confounding factors that may make interpretation difficult, but it seems to me that these differences at least deserve attention and follow up.

A.M. Geddes

I, in fact, am more involved in epidemiology than in pharmacokinetics and we have done just that. I can recall some excellent epidemiological studies, from the V.A. hospitals in the United States, about infections and changing use of antibiotics, that have been immensely valuable.

R.L. Galeazzi

A point that should be considered in envisaging dose-response studies in antimicrobial therapy is that the pattern of administration may have quite different consequences upon the therapeutic and the side effects of antibiotics. Consider, for instance, some penicillins. In some conditions the efficacy may be greater when they are given by constant infusion, but the incidence of leukopenia is then much greater.

J. Lahuerta

A particular clinical situation is that of prophylaxis, for instance in immunodepressed patients, who are at risk of deve-

loping systemic fungal or microbial infections. Although one may, for a particular drug, be sure of what the therapeutic range is for an acute infection, it is very difficult to decide on a prophylactic regime. Are there any clues to attempt to develop this?

A.M. Geddes

No, there are not. This is a very, very difficult problem.

L. Lemberger

In general, you alluded to what we do in the development of antimicrobials. We do dose-response curves, only we do them in the test tube. We do the MICs and then basically the clinical pharmacological evaluation of the drug is designed to give the medication in doses that will be safe to try and achieve blood levels, which will simulate the MIC. Hopefully then one will get tissue distribution, and so in a way dose-responses are taken care of indirectly, not against the host, but against the microbe which is actually the end result that you are looking for anyway.