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Can the Clinical Efficacy of Different Antibiotic Dosage Regimens in Gonorrhoea Be Predicted from the Gonocidal Effect of the Corresponding Plasma Level Profiles Simulated in vitro?

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Two different gonococcal strains with equal minimum inhibitory concentrations of ceftriaxone are exposed to continuously changing concentrations of this antibiotic simulating the ones found in man after the single intramuscular application of different doses (1 000, 250, 125, 50 and 25 mg). In general the bactericidal effect on both strains decreases more or less steadily with decreasing concentrations of ceftriaxone. One of the strains, however, shows a markedly dropped bactericidal effect as soon as the dosage is further reduced from 250 mg. These findings agree with previous experience from clinical dose-range finding studies. Thus the in vitro model presented here may be valuable for predicting both the optimum dosage and the clinical efficacy of new treatment protocols for gonorrhoea. *Key words: Ceftriaxone treatment of gonorrhoea; In vitro model for dose-range finding.*
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As a rule the decision to introduce a new antibiotic into the treatment of gonorrhoea is mainly based on its antibacterial effect in vitro as expressed by the minimum inhibitory concentration (MIC) and the plasma levels to be obtained in man. In general the conduct of a clinical trial is considered worthwhile if the plasma levels surpass the MIC for several hours. So far, however, it is unfortunately not feasible to predict from the pre-clinical data what the optimum dosage for gonorrhoea looks like. This problem is often circumvented by the application of very high, if not excessive, doses what may lead to a higher degree of side-effects. Recently Eichmann et al. (1) have conducted a systematic dose-range finding study in gonorrhoea. This study was based on the application of 50 to 500 mg ceftriaxone injected intramuscularly as a single dose. While the higher doses applied all turned out successful in every single case (in the meantime these findings have been confirmed (2, 3, 4, 5) on a broader scale) the same was not true facing the lowest dose (50 mg). Although the optimum dosage regimen of a given antibiotic in gonorrhoea can at least roughly be determined that way, such a trial is not so easy to perform these days. In the following we therefore describe an in vitro model which may be equally helpful in this context.

MATERIAL AND METHODS

Bacterial strains

Two gonococcal strains with identical MIC (0.008 μg/ml) recently isolated from clinical material were taken from the culture collection of the clinic (3067/83, 1608/83), one of them (the latter) producing beta-lactamase due to the nitrocefin test (6).

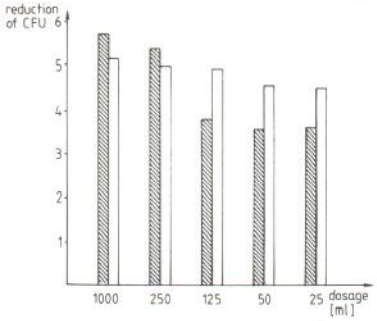


Fig. 1. Reduction of gonococcal density (CFU) given in orders of magnitude in the presence of various ceftriaxone concentration profiles with strain 1608/83 (hatched columns) and strain 3067/83 (blank columns).

Antibiotic and basic pharmacokinetic data

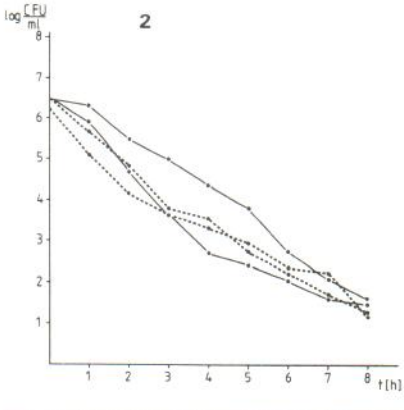
Ceftriaxone, a new third generation cephalosporin, highly resistant to beta-lactamase, was kindly donated by Roche, Grenzach-Wyhlen, FRG. The plasma levels of ceftriaxone after the intramuscular application of various doses could be determined on the basis of the findings in probationers after the injection of 1.5 g (7) due to the linearity of pharmacokinetics in the range investigated here.

Model apparatus

In a closed system gonococci are grown in broth and exposed over 8 hours to continuously changing concentrations of antibiotic representing the plasma level profile after the intramuscular injection of various doses (1 000, 250, 125, 50 and 25 mg) in man. At regular intervals the broth is checked for gonococcal density. The details of the mathematical basis and the practical performance of the experiments have already been described elsewhere (8). The clue parameters are given in Table I. All experiments were at least performed in duplicate (1 000, 250 mg) or even in triplicate (125, 50 and 25 mg).

RESULTS

In the presence of the ceftriaxone concentration profiles representing plasma levels after the injection of 1 000 and 250 mg respectively a dramatic reduction of gonococcal density was found with both strains (Figs. 1, 2 and 3). Although there was only a slight difference between the bactericidal effects of these two dosage regimens the higher dose was more effective than the lower one. This dose–effect relationship was also clearly found in the



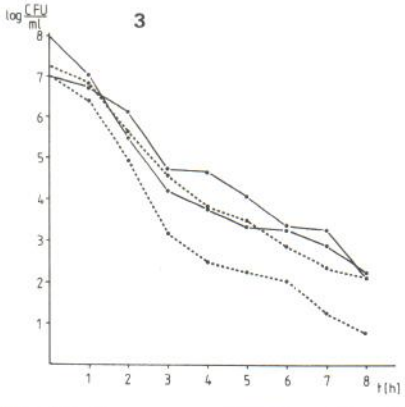


Fig. 2. Reduction of gonococcal density (log CFU/ml) in the presence of 1 000 mg (dotted lines) and 250 mg (continuous lines) with strain 3067/83.

Fig. 3. Reduction of gonococcal density (log CFU/ml) in the presence of 1 000 mg (dotted lines) and 250 mg (continuous lines) with strain 1608/83.

lower dose-range (Figs. 4 to 9). Between the two gonococcal strains, however, some difference became visible. While the bactericidal effect still declined almost steadily with further reduction of the dose (only the change from 125 to 50 mg was a little bit more marked) in strain 3067/83, a rather clear, but still limited reduction of antibacterial activity was seen with the other strain, when the dose of 250 mg was substituted by 125 mg.

DISCUSSION

Before a new antibiotic treatment protocol is introduced into the treatment of gonorrhoea on a broader scale its therapeutic safety margin should be elucidated, i.e. it should not only be known that it is effective in more than 95% of clinical cases (9), but also if the dosage chosen is close to the minimum required dose or not. From a general standpoint the ideal dosage should neither be too low (otherwise even a slow decrease of bacterial susceptibility would soon make dosage alterations inevitable as was the case with penicillin (10)) nor too high (otherwise the rate of unwanted effects could be increased). In principle dose-range finding studies as the one conducted by Eichmann et al. (1) constitute a good tool to obtain insight into the safety margin of a new treatment protocol. Studies of this type are, however, difficult to perform as many patients today are not willing to be included. For this reason some have tried to develop adequate animal models (11). With respect to gonorrhoea, however, it seems to be difficult if not impossible to find such a model. The animal models presented so far (12, 13, 14, 15, 16, 17, 18, 19) are either inapt for dose–effect studies or simply not feasible (20).

Facing this situation it seems helpful that the in vitro model applied here provides data which are at least to a certain extent predictive of clinical cure rates. In fact our preliminary data do not yet allow to state precisely what degrees of bactericidal activity are needed to ensure total clinical efficacy of a given dosage regimen. In general the results produced by the present in vitro model will be the more reliable the more different gonococcal strains are investigated. So far there is a good correlation with clinical experience: in the study performed by Eichmann et al. (1) many patients were still cured by as low a dose as 50 mg while one single patient remained uncured. In the present setting, fortunately, as few as two different strains sufficed to find one which was less well attacked by dosages from 125 mg downward (strain 1608/83). The obvious lack of a

Table I. *Modelling parameters for the simulation of different ceftriaxone concentration profiles after intramuscular application (all details are based on the fraction of 3.9% which is not bound to protein)*

Parameter		
Absorption rate constant K_1	(min^{-1})	0.029433
Elimination rate constant K_2	(min^{-1})	0.001446
Half-life of elimination $t_{1/2}$	(min)	479.4
Flow rate	(ml/min)	0.4338
Volume (V_A)	(ml)	300
Volume (V_B)	(ml)	14.74
Dose equivalent		
1 000 mg	(mg)	1.53
250 mg	(mg)	0.38
125 mg	(mg)	0.19
50 mg	(mg)	0.08
25 mg	(mg)	0.04

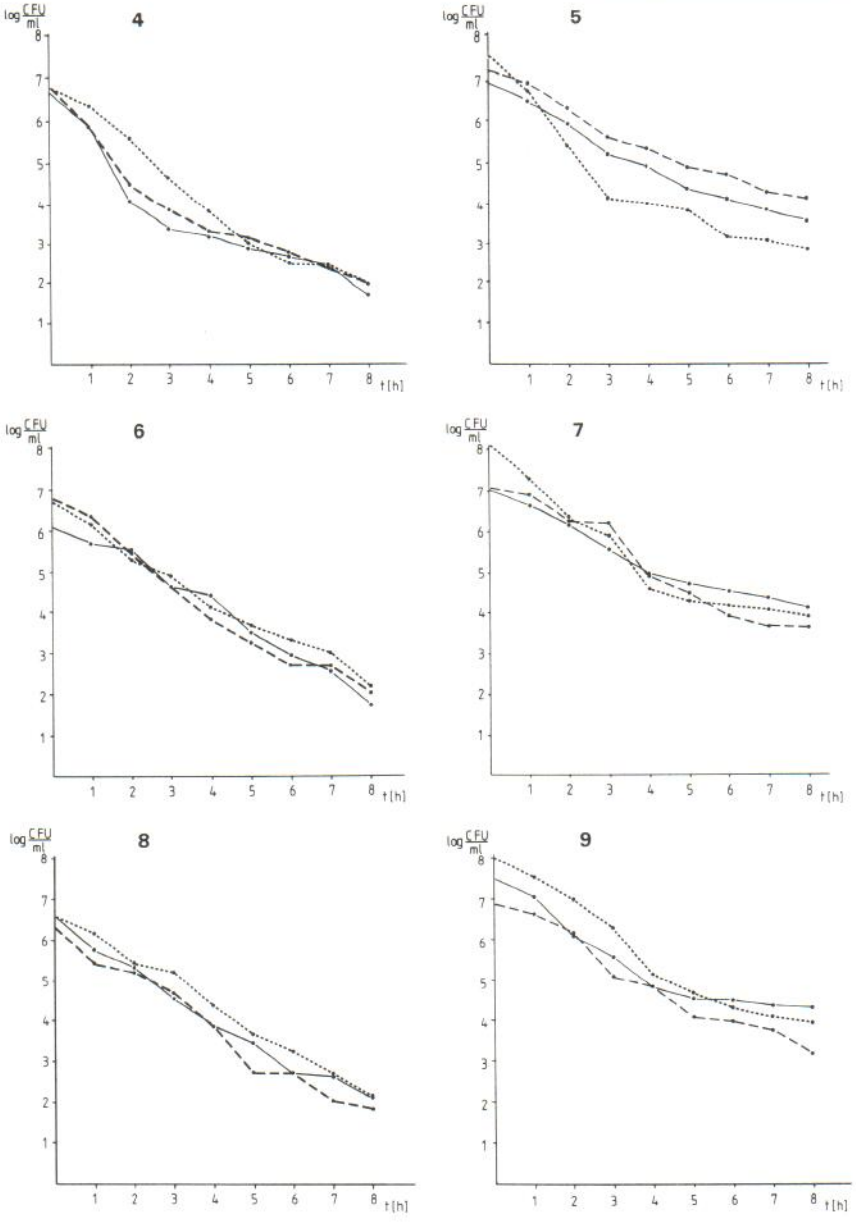


Fig. 4. Reduction of gonococcal density (log CFU/ml) in the presence of 125 mg with strain 3067/83.
Fig. 5. Reduction of gonococcal (log CFU/ml) in the presence of 125 mg with strain 1608/83.
Fig. 6. Reduction of gonococcal density (log CFU/ml) in the presence of 50 mg with strain 3067/83.
Fig. 7. Reduction of gonococcal density (log CFU/ml) in the presence of 50 mg with strain 1608/83.
Fig. 8. Reduction of gonococcal density (log CFU/ml) in the presence of 25 mg with strain 3067/83.
Fig. 9. Reduction of gonococcal density (log CFU/ml) in the presence of 25 mg with strain 1608/83.

dramatic loss of efficacy between any two doses investigated also correlates well with the clinical experience: due to the study by Eichmann et al. (1) the reduction of the dose from 125 to 50 mg did not lead to a total loss of efficacy but to a partial one. It is tempting to speculate that the gonococcal strain isolated from the one unhealed patient would show less susceptibility in the present in vitro model than all the other ones. This feature is at the moment under investigation in our clinic.

If it is possible at all to draw any general conclusions from the still limited data presented here they could read: if a new antibiotic seems to be useful for the treatment of gonorrhoea on the basis of its MIC values and pharmacokinetic properties, various doses should be tested by the in vitro model presented here and the one chosen for clinical trial which is just above the range where bactericidal effects tend to decrease more than steadily in at least one of the gonococcal strains investigated.

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