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Pharmacokinetics of long half-life antibacterials*

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Trimethoprim (TMP), sulfamethoxazole (SMZ) and sulfadiazine (SDZ) are characterized by elimination half-lives of 9 to 15 h. Effective serum concentrations can therefore be maintained by twice daily administration, but without a loading dose steady state levels will be reached only after 3 days. Renal disease has little effect on the pharmacokinetics of unchanged SMZ, whereas TMP and SDZ elimination is prolonged in uremia. Dosage adaptation to creatinine clearance is difficult, since the ratio of the two components in serum and urine will be altered. Abnormal drug accumulation in liver disease during a treatment with TMP and SMZ has not been demonstrated.

Die Halbwertszeiten von Trimethoprim (TMP), Sulfamethoxazol (SMZ) und Sulfadiazin (SDZ) liegen zwischen 9 und 15 h. Dank dieser langsamen Elimination können therapeutisch wirksame Serumkonzentrationen durch 12-stündliche Medikamentengaben aufrecht erhalten werden. Ein 'steady-state' wird allerdings erst nach 3 Tagen erreicht, weshalb eine initiale Sättigungsdosis erforderlich sein kann. Bei Niereninsuffizienz bleibt die Halbwertszeit des SMZ unverändert, wogegen die Elimination des TMP und des SDZ bei Urämie verzögert sind. Bei den fixen TMP/SMZ-Kombinationen ist eine Dosisanpassung bei stark verminderter Kreatinin-Clearance problematisch, da das Verhältnis der einzelnen Komponenten infolge ihrer unterschiedlichen Kinetik gegenüber der Norm verändert wird. Eine abnorme Akkumulation dieser Medikamente bei Leberkrankheiten wurde hingegen bis jetzt nicht beobachtet.

Introduction

A correlation between pharmacodynamic or therapeutic effects and serum concentrations has been demonstrated for several drugs. In chemotherapy with reversibly acting bacteristatic agents a minimum inhibitory concentration in the blood should be reached and maintained for the duration of treatment. Therefore, the choice of dosage regimens can become a critical factor for therapeutic success or failure. The knowledge of the time course of drug absorption, distribution, metabolism and excretion will greatly help the clinician to make rational decisions concerning the

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optimal dose and dosing interval. Among the different pharmacokinetic parameters the elimination half-life ($t_{\frac{1}{2}}$), the volume of distribution (V_d) and the fractional elimination of unchanged drug in the urine (f_r) are of special interest for calculations of dosage schedules in different clinical situations.

Half-life and drug accumulation

The elimination half-life, i.e. the time required for the drug level to decrease by 50%, gives an indication about the duration of action following a single dose and determines the course and extent of drug accumulation following repetitive administration. In the following discussion the half-life during the post-distribution phase (β) is employed, since kinetic data of folate inhibitors were usually analysed by an open one compartment model.

Trimethoprim (TMP) and the sulphonamides in the current antibacterial combinations are characterized by considerably longer half-lives than most other antibiotics. In subjects with normal renal function the range of mean $t_{\frac{1}{2}}$ values was 9 to 14 h for TMP, 9 to 11 h sulphamethoxazole (SMZ) (Craig & Kunin, 1973; Kaplan *et al.*, 1973; Rieder *et al.*, 1974; Zech *et al.*, 1978), 10 to 15 h for sulfadiazine (SDZ) (Andreasen *et al.*, 1978; Ohnhaus & Spring, 1975) and 9 to 11 h for sulfamoxole (SMO) (Kuhne *et al.*, 1976). The obvious advantage of the relatively slow elimination is the possibility to maintain therapeutic serum levels by administration every 12 h. Besides being practical, this dosage regimen also prevents abnormal drug accumulation. The so called accumulation factor *R*, i.e. the relationship between drug amount in the body at steady state (m_{ss}) and the maintenance dose *(D)*, depends only on the relative dosing interval $\varepsilon = \tau/t_{\frac{1}{2}}$ (Kruger-Thiemen, 1960):

$$R = \frac{m_{ss}}{D} = \frac{1}{1-2^{-\varepsilon}} \approx 1{\cdot}44\, t_{\frac{1}{2}}/\tau$$

Thus, as long as $t_{\frac{1}{2}}$ and dosing interval (τ) remain in the same range, accumulation will not occur to any clinically relevant degree.

Another practical problem to be considered with slowly eliminated drugs is the need for an initial loading dose. Since steady state serum concentration (C_{ss}) will only be reached after five half-lives, a treatment starting with a usual maintenance dose might be inadequate, when immediate therapeutic action is required. In the case of trimethoprim–sulphonamide combination C_{ss} is usually not achieved before 48 h. While this delay can be accepted in many clinical situations a loading dose must be given in patients with renal disease in whom the dosing interval is prolonged or the maintenance dose reduced.

Finally the influence of age on the rate of sulphonamide elimination should be remembered. The $t_{\frac{1}{2}}$ in infants less than 10 days old is longer than in adults, it then rapidly decreases during the next weeks to remain at a lower level until the age of 6 to 8 years (Krauer & Dettli, 1969; Krauer, Spring & Dettli, 1968). The recommended dose is therefore proportionally greater for the age group between 6 months and 5 years than for adults (Fowle *et al.*, 1975).

Modes of elimination

The main routes of elimination for drugs are renal excretion and hepatic metabolism. The relative importance of these mechanisms for different drugs and

patient groups can be easily estimated by measuring the fraction of absorbed dose which is eliminated unchanged in the urine. This 'renal dose fraction' f_r is one of the most useful pharmacokinetic parameters, which allows prediction of altered drug elimination in renal disease (Dettli & Tschanz, 1976).

Trimethoprim and sulphonamide elimination depend both on hepatic metabolism and renal excretion. Urinary elimination of unchanged drug in patients with normal renal function amounts to 53 to 67% for TMP (Craig & Kunin, 1973; Kaplan *et al.*, 1973; Rieder *et al.*, 1974), 15–30% for SMZ (Craig & Kunin, 1973; Kaplan *et al.*, 1973; Ohnhaus & Spring, 1975), 50 to 54% for SDZ (Andreasen *et al.*, 1978; Ohnhaus & Spring, 1975) and 34% for SMO (Kuhne *et al.*, 1976). Most of the metabolites are pharmacologically inactive.

An important factor in the renal excretion of these folate inhibitors is the urinary pH value. Since the sulphonamides are weak acids (pKa 5·6 to 6·5) their non-ionic tubular reabsorption decreases by alkalinisation of the urine, whereas trimethoprim is a weak base (pKa 7·3) and its tubular reabsorption decreases by acidification of the urine. The half-life of elimination is not significantly modified by urinary pH variation, but the relative amounts of active drug in the urine are considerably altered (Craig & Kunin, 1973). This factor should therefore be taken into consideration when experimental data are compared.

Influence of renal and hepatic disease on the pharmacokinetics of trimethoprim and sulphonamides

Impaired kidney function is one of the most frequent causes of abnormal drug accumulation. The relationship between the glomerular filtration rate and renal excretion has therefore been studied for a great number of drugs (Dettli, 1977). A basic assumption in such investigations is, that a linear relationship exists between endogenous creatinine clearance (Cl_{cr}) and elimination rate constant *(k)*:

$$k = k_{nr} + \alpha\, Cl_{cr}$$

where k_{nr} is the rate constant of extrarenal elimination and α a proportionality factor. Values for k_{nr} and α can be determined for different drugs by measuring elimination rate constants in patients with various degrees of clearance reduction. The use of elimination rate constant *(k)* instead of half-life for comparison with renal function is preferable, since instead of the simple linear regression line a complex hyperbolic curve is found when $t_{\frac{1}{2}}$ and Cl_{cr} are graphically related.

The influence of renal disease on the pharmacokinetics of the TMP–SMZ combination has been studied by several authors (Baethke, Golde & Gahl, 1972; Rieder *et al.*, 1974; Zech *et al.*, 1978). As it could be predicted from the low f_r value for unchanged SMZ, the elimination of this drug was little altered by renal function: Half lives in uremic patients were not longer than 13·3 to 18·8 h (means). However, the elimination rate of sulphonamide metabolites in patients with creatinine clearance below 5 ml/min approached zero and a marked accumulation occurred. In these studies the elimination of TMP was found to be definitely prolonged in cases with Cl_{cr} below 10 ml/min: mean $t_{\frac{1}{2}}$ increased to 26 to 37 h (Rieder *et al.*, 1974; Zech *et al.*, 1978). The use of SMZ–TMP combination in patients with severe renal disease is therefore problematical. Even if a careful dosage reduction according to a

Cl_{cr} value is attempted, the proportion of the bacteriologically active components can be quite different from normal and SMZ metabolites will reach very high levels.

From a pharmacokinetic point of view sulfadiazine could be a more suitable candidate for combination with trimethoprim in the treatment of infections in patients with renal disease. Elimination rates of SDZ in cases with different degrees of clearance reduction are similar to that of TMP (Ohnhaus & Spring, 1975; Bergan, Vik-Mo, & Anstad, 1977). The ratio of the extrarenal elimination rate constant k_{nr}, which is equal to the elimination rate constant in anuric patients, and the overall normal elimination rate constant (k_n) is about 0·45 for both drugs. Since $k_{nr}/k_n = Qo$ is also linearly related to creatinine clearance, dosage adaptation in renal disease can be performed with simple nomograms (Dettli & Tschanz, 1976). In contrast to SMZ–TMP a combination of SDZ–TMP would require a dosage reduction by the same proportion for both components.

The kinetics of trimethoprim and sulphonamides in liver disease have been less well investigated than in renal disease. Rieder & Schwartz (1975) found in 7 patients with advanced liver damage no direct evidence for prolonged elimination of SMZ or TMP: the mean half-lives of 10·1 and 14·3 h respectively were similar to that in control subjects. Also the ratio of metabolized to unchanged sulphamethoxazole remained in the normal range. In a recent study by Neuman & Fluteau (1978) trimethoprim and sulphamoxole serum levels following repeated administration to 4 cases with liver cirrhosis were not significantly different from serum levels in control subjects. These studies indicate that administration of antibacterial folate inhibitors in patients with liver disease is probably without particular risk of accumulation. However, the problem of trimethoprim and sulfonamide metabolism in chronic liver disease should be further evaluated.

The pharmacokinetic properties of sulfonamides and diaminopyrimidines should be carefully considered before they are used in fixed drug combinations. Substances with identical kinetic behaviour have the advantage to ensure an optimal serum and urinary concentration ratio for antibacterial synergism, which is maintained in patients with impaired drug elimination mechanisms.

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Discussion

Professor Asscher, Cardiff. One aspect of clearance of trimethoprim and sulphonamide to which Dr Follath did not refer was urine flow rate. Does he think that is of importance? I recall that trimethoprim excretion is highly flow rate-dependent, whereas the sulphonamide component is not so much affected by urine flow. I believe this was shown by Sharpstone (1969).

Dr Follath. That is right. Flow rate influences the elimination of these drugs, but it was shown that this factor is not important clinically. The same applies to urine pH. Although Craig & Kunin (1973) have demonstrated that a pH dependent elimination clearly exists, the half-lives in the various patient groups were found to remain in the same range. This means that urine flow rate will not influence the dosage schedule, but it should be considered when pharmacokinetic data from different authors are compared.

Professor Turner, London. Protein binding of those drugs was similar, but the volume of distribution was markedly different. Could Dr Follath postulate the different factors responsible for the volume of distribution?

Dr Follath. The volume of distribution is higher with trimethoprim, which may indicate that its concentration in the various tissues is also different from that of

sulphonamides. The volume of distribution is influenced by different factors, such as lipid solubility and specific binding affinity of the various tissues.

Professor Brumfitt. Dr Follath told us that there was no difference in the half-life in advanced liver disease and normal liver. Has he studied the liver 'excretion'—if I may use that term—either by retrograde endoscopy, puncture of the bile duct at operation, duodenoscopy or any of the other techniques?

Dr Follath. I have not studied any of these drugs myself. The only paper I have found on this subject is that by Rieder & Schwartz (1974). They measured serum levels in control patients and in patients with liver disease. The techniques mentioned by Professor Brumfitt were not used.

Dr Bergan. The explanation for the higher distribution volume of trimethoprim compared to sulphonamides is that trimethoprim penetrates better into the cells of the body.

Dr Follath. This, again, is a consequence of lipid solubility of a drug. Highly lipid soluble drugs will obviously penetrate cell membranes better than lipid insoluble ones.

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