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Variability of Serum Concentrations of Trimethoprim and Sulfamethoxazole during High Dose Therapy

Summary: Serum kinetics of trimethoprim and sulfamethoxazole were studied in 23 patients during oral and i.v. treatment of *Pneumocystis carinii* pneumonia. Daily doses of 15–22 mg/kg trimethoprim and 75–110 mg/kg sulfamethoxazole were given every 6 h. Despite administration of a loading dose of twice the regular dose, serum trough concentrations continuously rose from 12 h to 96 h by 63% for trimethoprim and 102% for sulfamethoxazole. After 4–6 days mean trough concentrations of trimethoprim and sulfamethoxazole were 7.7 ± 3.0 and 198 ± 74 mg/l, with individual values of < 4.6 and < 103 mg/l in two patients and > 11.4 and > 307 mg/l in two others. Patients treated orally or i. v. had similar serum levels. However, large interindividual variability was observed despite weight-specific dosing. Administration of a loading dose did not prevent accumulation of serum levels of trimethoprim and sulfamethoxazole over several days of treatment.

Zusammenfassung: *Variabilität der Serumkonzentrationen von Trimethoprim und Sulfamethoxazol bei hochdosierter Therapie.* Die Serumkinetik von Trimethoprim und Sulfamethoxazol wurde bei 23 Patienten während oraler oder parenteraler Behandlung von *Pneumocystis carinii*-Pneumonien untersucht. Tagesdosen von 15–22 mg/kg Trimethoprim und 75–110 mg/kg Sulfamethoxazol wurden in Intervallen von 6 Stunden verabreicht. Trotz der Verabreichung von Ladungsdosen, die dem Zweifachen der Einzeldosen entsprachen, stiegen die Talspiegel im Serum zwischen 12 und 96 h bei Trimethoprim um 63% und bei Sulfamethoxazol um 102% an. Nach 4 bis 6 Tagen betrugen die mittleren Talkonzentrationen bei Trimethoprim 7.7 ± 3.0 und bei Sulfamethoxazol 198 ± 74 mg/l, mit Einzelwerten von < 4.6 und < 103 mg/l Trimethoprim sowie > 11.4 und > 307 mg/l Sulfamethoxazol bei je zwei Patienten. Trotz gewichtsspezifischer Dosierung wurde eine große interindividuelle Variabilität beobachtet. Oral und parenteral behandelte Patienten wiesen vergleichbare Konzentrationen auf. Die Verabreichung der Ladungsdosen konnte eine Akkumulation von Trimethoprim und Sulfamethoxazol während der ersten Tage der Behandlung nicht verhindern.

Introduction

Trimethoprim and sulfamethoxazole in doses of 15–20 mg/kg/d and 75–100 mg/kg/d are considered the standard initial therapy of *Pneumocystis carinii* pneumonia [1–3]. However, because of the high incidence and severity of side effects only 43%–66% of patients can complete the 3-week course of therapy [4–6]. Dose reduction and monitoring of drug levels or shortening the duration of high dose therapy have therefore been attempted to reduce the rate of toxicity, but have yielded only limited success [7–9].

The present, prospective study examined the pharmacokinetics of trimethoprim and sulfamethoxazole during the first week of treatment to further elucidate accumulation of trimethoprim, sulfamethoxazole or the N-acetyl metabolite of sulfamethoxazole and to serve as a basis for improved patients' management. The influence of weight-specific dosing on the interindividual variability of steady state concentrations was studied. In addition, a loading dose to more rapidly achieve steady state was administered, since the long half-lives of trimethoprim and sulfamethoxazole would favour such a concept. So far this concept has not been addressed during high-dose therapy of trimethoprim and sulfamethoxazole.

Patients and Methods

One woman and 22 men suffering from HIV-associated *P. carinii* pneumonia were enrolled in the study. The mean age of the patients was 40 (range 24–75) years the mean weight 59 (42–80) kg. At the onset of treatment, serum creatinine averaged 101 µmol/l (72–125), lactate dehydrogenase 512 U/l (306–995), and aspartate aminotransferase 58 U/l (14–397).

Daily doses of 15–22 mg/kg trimethoprim and 75–110 mg/kg sulfamethoxazole were administered to 15 patients orally and to eight patients by intravenous infusions. The dosing interval was 6 h. Therapy was started with a loading dose of twice the regular dose. Blood samples were taken as trough levels before the subsequent dose. From 11 patients four to seven samples were obtained to document the increase of serum levels within the first 6 days of treatment. In all 23 patients at least one sample was obtained between days 4 and 6.

A high-pressure liquid chromatography system consisting of a model 6000 A pump, a Wisp 710 B automatic sample processor, and a model 990 photodiode array detector (Waters Associates,

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Milford, Mass., USA) was used to analyze the serum samples. Analytical grade reagents (Fluka AG, Buchs, Switzerland), HPLC grade solvents (Rathburn Ltd., Walkerburn, Scotland, UK) and double-distilled water were used. The mobile phase was prepared by dissolving 1.16 g potassium dihydrogen phosphate in 850 ml of water, adjusting to pH 3.0 with o-phosphoric acid (85%, 80 µl) and adding 150 ml of acetonitrile. Particulate matters and dissolved gases were removed by vacuum filtration through a fluorocarbon membrane filter (FHUP, 0.5 µm, Millipore Corp., Bedford, Mass.). Chromatography was performed at ambient temperature using a reversed phase Nova-Pak C18 column, (15 cm by 3.9 mm, 5 µm particles, Waters) and a flow rate of 1.6 ml/min. The retention times of trimethoprim, sulfamethoxazole, and N-acetyl-sulfamethoxazole were 2.1, 3.0, and 4.6 min, respectively. Total analysis time was 6 min per sample. External standards containing 10 mg/l of trimethoprim and 200 mg/l of sulfamethoxazole were prepared. Standards and serum samples (0.1 ml) were thoroughly mixed with 0.5 ml of 0.33 M perchloric acid to precipitate the proteins. After centrifugation, 15 µl of the clear supernatant was injected. Concentrations were calculated by comparing the peak area of each substance with those of the standards. The specific UV-absorbance of sulfamethoxazole and its N-acetyl metabolite was equal at 265 nm, whereas chromatograms at 230 nm were used to determine trimethoprim. Detection limits of the assay were 0.5 mg/l for trimethoprim and 1 mg/l for sulfamethoxazole and its N-acetyl metabolite. Linearity of the assay was tested at concentrations ranging from 0.4 to 40 mg/l for trimethoprim and from 2.4 to 286 mg/l for sulfamethoxazole. Coefficients of correlation of > 0.9998 were found. Recoveries from spiked serum samples were > 94%. Precision was determined by 12 repeated assays each at 200 mg/l and 50 mg/l of sulfamethoxazole, and at 10 mg/l and 2.5 mg/l of trimethoprim. The coefficients of variation were 1.3%, 1.8%, 1.5%, and 2.3%, respectively.

Results

Trough steady state concentrations, determined 4 to 6 days after the initiation of therapy, varied within a wide range for both trimethoprim (mean ± standard deviation 7.7 ± 3.0 mg/l, range 2.5–12.6 mg/l) and sulfamethoxazole (198 ± 74 mg/l, 63–310 mg/l). Concentrations of trimethoprim and sulfamethoxazole were < 4.6 and < 103 mg/l in two patients and > 11.4 and > 307 mg/l in two others (Figure 1). The ratio of the serum levels of both drugs was also highly variable, ranging from 11 to 54 (mean sulfamethoxazole/trimethoprim ratio 28 ± 10). Similar results were observed with both routes of administration. During oral and i. v. therapy mean trough concentrations (± SD) of trimethoprim were 7.6 ± 3.4 and 7.8 ± 2.3 mg/l and concentrations of sulfamethoxazole were 202 ± 78 and 190 ± 71 mg/l, respectively.

No significant correlation was found between various dosing or laboratory parameters (age, dose, dose/kg, weight, creatinine, lactate dehydrogenase, aspartate aminotransferase) and steady state concentrations of trimethoprim or sulfamethoxazole, as determined by stepwise regression analysis. Correlation coefficients determined by linear regression analysis revealed that each of these parameters contributed individually to < 25% of the total variability observed with either drug. Zidovudine treatment or intravenous use of illicit drugs also had no significant

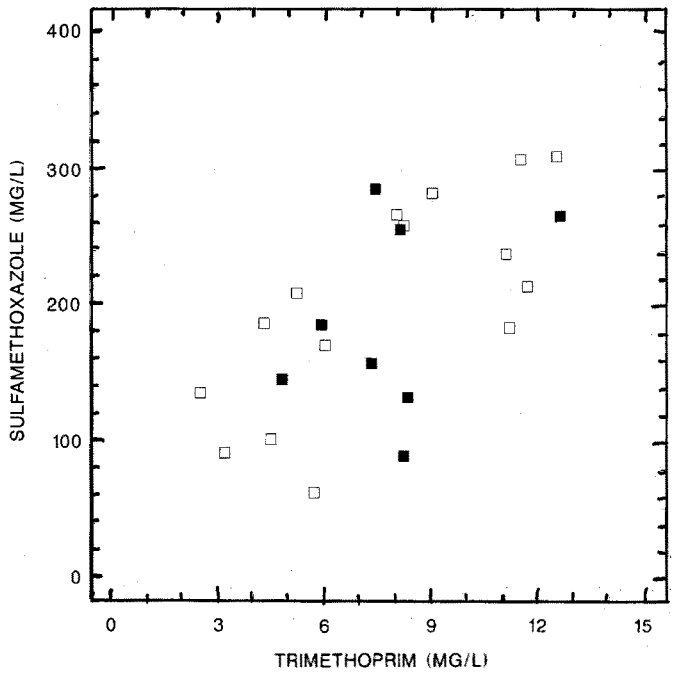

Figure 1: Serum trough concentrations of trimethoprim and sulfamethoxazole determined after 4–6 days of high dose therapy. Full symbols relate to i. v. administration, open symbols to oral administration.

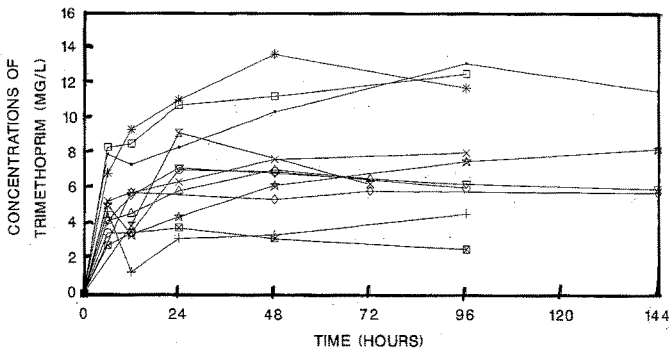

Figure 2: Increase of serum trough levels during high dose therapy with trimethoprim (15–22 mg/kg/d) given in intervals of 6 h. Therapy was started with a loading dose of twice the regular single dose.

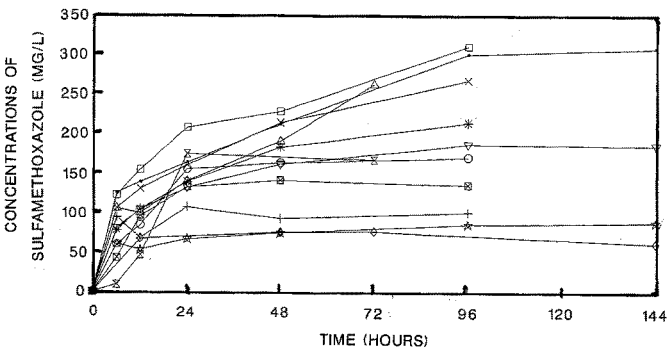

Figure 3: Increase of serum trough levels during high dose therapy with sulfamethoxazole (75–110 mg/kg/d) given in intervals of 6 h. Therapy was started with a loading dose of twice the regular single dose.

influence on drug levels. A significant correlation was found between the steady state levels of trimethoprim and sulfamethoxazole ($r = 0.64$, $p < 0.01$).

The ratio of N-acetyl-sulfamethoxazole to sulfamethoxazole determined after 4–6 days of treatment was 13.3 ± 5.5%. A significant correlation between N-acetyl-sulfamethoxazole and serum creatinine was found ($r = 0.75$).

The loading dose of twice the regular dose was too low to achieve steady state rapidly (Figures 2, 3). Trimethoprim trough levels increased from 5.7 ± 2.7 mg/l after 12 h to 7.1 ± 2.6 after 24 h up to 9.3 ± 3.0 after 96 h. The respective data for sulfamethoxazole were 107 ± 33, 155 ± 34, and 216 ± 74 mg/l.

Discussion

This study documents a remarkable interindividual variability of serum concentrations of trimethoprim and sulfamethoxazole during treatment of *P. carinii* pneumonia with high doses of co-trimoxazole. The variability of the serum kinetics occurred despite controlled administration and weight-specific dosing, and did not correlate with variations of various laboratory or clinical parameters.

Similar ranges of serum levels of trimethoprim and sulfamethoxazole have also been observed in other clinical studies. Equivalent doses (15–20 mg/kg/d of trimethoprim) were studied in 18 patients by an Australian group [10, 11]. Serum levels 1.5 h post dose on days 2–4 ranged from 3.1 to 11.0 for trimethoprim and from 155 to 317 mg/l for sulfamethoxazole. *Wörber* et al. reported median trough levels of 7.5 (trimethoprim) and 200 mg/l (sulfamethoxazole) in a less homogeneous group of 14 patients receiving a median daily dose of 19 and 96 mg/kg, respectively [12]. Concentrations of trimethoprim, sulfamethoxazole, and N-acetyl-sulfamethoxazole have also been measured in 11 patients participating in a double-blind comparison with trimethoprim and dapsone [5, 6]. Trimethoprim and sulfamethoxazole were administered orally every 6 h in daily doses of 20 and 100 mg/kg. However, no loading doses were administered in these studies. Mean 2 h post dose peak plasma concentrations increased from day 3 to day 7 and 14 from 11.2 ± 3.9 to 12.4 ± 4.5 and 12.7 ± 6.6 mg/l for trimethoprim and from 271 ± 86 to 284 ± 70 and 317 ± 152 mg/l for sulfamethoxazole, respectively. Sulfamethoxazole/trimethoprim ratios ranged from 14 to 51, mean N-acetyl-sulfamethoxazole levels were 11.5% of the mean sulfamethoxazole levels on day 7.

Oral and intravenous administration resulted in similar mean concentrations. Rapid absorption of high dose trimethoprim and sulfamethoxazole was shown by both single [13] and multiple dose [14] pharmacokinetic studies in healthy volunteers. Prolonged mean half-lives have been reported by *Winston* et al., but not by *Siber* et al., in non-AIDS-patients with normal renal function treated intravenously with high doses of trimethoprim and sulfamethoxazole [15, 16]. However, even at regular elimination half-lives of 8–10 h, as observed following administration of a standard single dose of trimethoprim or sulfamethoxazole, accumulation of serum levels has to be expected within the first days at dosing intervals of 6 h [17]. It has been postulated that hepatic metabolism might possibly be altered in AIDS patients [5]. However, the mean proportion of the most abundant metabolite, N-acetyl-sulfamethoxazole, was 13.5% of sulfamethoxazole in 12 healthy subjects [14], which is comparable to data obtained in the present study as well as by *Lee* et al. in AIDS patients [5]. Nevertheless, it is conceivable that saturation of the enzyme systems during high dose therapy could lead to a nonlinear dose response in some patients. Thus, interindividual variations in nonrenal clearance may be a factor contributing to variability.

Very high loading doses would be required to rapidly achieve steady state. Doubling of the initial dose was clearly insufficient in the present study. However, in defining an optimal loading dose more than pharmacokinetics need to be considered. There is a limit to the total number of pills that a patient can swallow within a few minutes or hours and frequency and severity of gastrointestinal side effects increase with increased loading doses. Future studies are required to determine whether therapeutic drug monitoring with consecutive dose reductions might reduce toxicity while preserving clinical efficacy. Although the frequency of adverse effects, such as gastrointestinal or hematological toxicity, seems to be dose related, only limited knowledge exists which of the two drugs, if any, should be monitored and which serum levels represent the optimal therapeutic range. While maintaining serum concentration of trimethoprim between 5 and 8 mg/l enabled all patients to complete the full treatment course [9], most adverse effects seem to be caused by sulfamethoxazole or its metabolites [18]. However, insufficient experimental and clinical data are available on the minimal or optimal concentrations required for effective therapy.

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Information

Stipendium der Walter-Marget-Vereinigung zur Förderung der Infektiologie e.V. gemeinsam mit dem SmithKline Beecham Stipendium zur Erforschung von Staphylokokken-Infektionen

Ausschreibung eines Stipendiums

Die Walter-Marget-Vereinigung zur Förderung der Infektiologie e.V. vergibt zusammen mit SmithKline Beecham Pharma ein Stipendium für Forschungsarbeiten zum Thema Staphylokokken-Infektionen, um die wissenschaftliche Ausbildung junger Ärztinnen und Ärzte zu fördern. Das Stipendium ist sowohl für klinische als auch für experimentelle Arbeiten zum Thema Staphylokokken ausgeschrieben.

Um das Stipendium können sich Ärztinnen/Ärzte bewerben, die

als Ärztin/Arzt für die Dauer des Stipendiums und weitere fünf Jahre einen Arbeitsvertrag an einer deutschen Klinik haben, der auch für die Dauer des Stipendiums und des damit verbundenen Aufenthaltes an dem der Ausbildung dienenden Platz aufrecht erhalten bleibt,
durch wissenschaftliche Arbeiten ihr besonderes Interesse am Arbeitsgebiet bereits dokumentiert haben,
zu einem Studienaufenthalt bis zu einem Jahr an einer für die Fortbildung im Arbeitsgebiet Staphylokokken besonders geeigneten Klinik oder Institution im In- oder Ausland bereit sind,
im Rahmen der Möglichkeiten durch einen Eigenbeitrag an den Gesamtkosten des Studienaufenthaltes beitragen wollen,
nicht älter als 40 Jahre sind.

Bewerbungsunterlagen sind bis zum 30. September 1993 zu richten an:
Walter-Marget-Vereinigung zur
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