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High Dose Treatment with Antibiotics in Cystic Fibrosis – A Reappraisal with Special Reference to the Pharmacokinetics of Betalactams and New Fluoroquinolones in Adult CF-Patients

Summary: In this review we analyzed the pharmacokinetic basis for high dose treatment with antibiotics of patients with cystic fibrosis. Both our results and those from other well designed pharmacokinetic studies do not support the view that low blood levels of antibacterials are a common feature of CF. We were unable to detect a decrease in absorption, nor could we find evidence for enhanced elimination of antibacterials in CF. Both these factors have been considered responsible for reducing the plasma (and tissue) levels of antibiotics. Most recent studies on kidney function are in agreement with these findings, since neither inulin nor creatinine clearance differ between CF-patients and healthy volunteers. In contrast to previous discussion, the volume of distribution (Vd_{ss}) was not elevated for any compound. The rational of weight correction of volume terms like Vdss or total clearance has never been clearly demonstrated and should therefore not be used without prior proof of relevance. Since the variability of pharmacokinetic parameters of antibiotics in CF-patients may be considerable, we suggest that a dose increase of 20–30% may be justified, but cannot agree with two to fourfold increases in dosage as previously proposed and applied in many CF-centers. Until more findings become available for non-adult CF-patients, these conclusions are only valid for adult CF-patients.

Zusammenfassung: *Antibiotika-Hochdosis-Therapie bei Patienten mit zystischer Fibrose – Kritische Revision unter besonderer Berücksichtigung der Pharmakokinetik der β-Laktame und der neuen fluorierten Chinolone bei erwachsenen CF-Patienten.* In dieser Übersichtsarbeit wurde von uns die Grundlage der Hochdosierungstherapie von Antibiotika bei Mukoviszidose kritisch analysiert. Wir verwendeten sowohl Daten aus der Literatur als auch eigene Ergebnisse. Weder die Literaturdaten, die von uns geforderte Kriterien für Vergleichbarkeit erfüllen, noch unsere eigenen Daten haben Hinweise für generell niedrige Plasmaspiegel von Antibiotoka bei Mukoviszidose-Patienten ergeben. Wir haben außerdem nicht zeigen können, daß die Resorption verringert oder die Elimination beschleunigt ist. Beides würde die Plasma-(Gewebs-) Spiegel von Antibiotika erniedrigen. Neuere Untersuchungen zur Nierenfunktion bestätigen diese Ergebnisse, da sich weder die Inulin- noch die Kreatinin-Clearance von CF-Patienten und Gesunden unterschied. Auch die Verteilungsvolumina der Antibiotika waren nicht erhöht, wie das oft diskutiert worden war. Wir haben außerdem die Grundlagen für die oft praktizierte Gewichtskorrektur von Volumenparametern wie Cl_{tot} oder Vd_{ss} analysiert und sind zu dem Ergebnis gekommen, daß man nicht ungeprüft annehmen kann, daß eine Gewichtskorrektur dieser Volumenparameter für jede Substanz sinnvoll ist. Um die jedoch vorhandene beträchtliche Variabilität der pharmakokinetischen Parameter von Antibiotika bei Mukoviszidose-Patienten ausgleichen zu können, schlagen wir eine Dosiserhöhung um 20 bis 30% vor. Eine Dosiserhöhung um das Zwei- bis Vierfache, wie bisher vorgeschlagen und in vielen CF-Zentren durchgeführt, ist jedoch nach unserer Ansicht nicht gerechtfertigt. Bevor nicht ähnliche Untersuchungen auch bei nicht-erwachsenen CF-Patienten vorliegen, gelten die hier gemachten Dosierungsvorschläge nur für erwachsene Mukoviszidose-Patienten.

Introduction

Numerous publications and reviews (1–4) have suggested in the past that patients with cystic fibrosis (CF) require higher doses of antibiotics than other individuals. Lower blood levels as a consequence of enhanced elimination and/or impaired absorption of antibiotics were reported and even a well respected journal such as the *Lancet* supported that view in a recent editorial (5).

The index paper for this was published in 1975 by *Jusko* et al. (6) in which the authors showed that the elimination of dicloxacillin is more rapid in patients with CF than in healthy volunteers. That report was followed two years later by a similar investigation by the same group with

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methicillin (7) in which the increase in elimination was certainly not as impressive as in their previous paper on dicloxacillin (6).

Except for enhanced elimination of antibiotics, reduced absorption of antibiotics has long been believed to be a consequence of the gastrointestinal affections observed in CF-patients (8). That assumption, however, was made following findings of decreased fat and vitamin absorption (9–11) and a short comment by *Guggenbichler* et al. (12) in their report on epicillin pharmacokinetics in patients with cystic fibrosis. Administration of higher doses of antibiotics, therefore, seemed only logical in this context.

Another reason for high dose treatment with antibiotics depended on the assumption that the higher plasma concentrations lead to higher antimicrobial activity at the site of infection, presumably the bronchial secretions. Since bronchial secretions cannot be collected very easily, sputum was often used as a specimen reflecting the concentrations at the site of infection. Apart from this rather unrealistic assumption, no study has ever shown that effective sputum concentrations may be consistently achieved in CF-patients, nor has any report demonstrated that the sputum concentrations are important indicators of a sufficient antimicrobial effect in the CF-lung.

Since we agreed with the *Lancet* that the "treatment of *Pseudomonas aeruginosa* infection has emerged as one of the greatest challenges in the management of cystic fibrosis" (5) we felt that it was time to critically analyze the pharmacokinetic basis of antimicrobial treatment in CF. This article will review and analyze the pitfalls of previous studies and deduct conclusions only from those studies that have been adequately designed and have used competent pharmacokinetic and statistical analysis for interpretation. In addition, we will include abstracts of our most recent work on the pharmacokinetics of β-lactams and new fluoroquinolones in adult CF-patients.

Previous Investigations

We will analyze previous investigations on the basis of the following aspects:

- Use of adequate control and CF-patient groups;
- Variability of data for CF-patients due to different investigators;
- Pharmacokinetic calculations and pharmacokinetic concepts;
- Analysis of antimicrobials in biological specimens.

Our Studies

We will then describe the criteria for our studies:

- Control and CF-patient groups;
- Identical chemical analysis, quality control, pharmacokinetic calculations and statistics.

Previous Investigations

Use of Adequate Control and CF-patient Groups

Many studies published before 1984 do not include control groups at all, instead making comparisons with data from literature. In view of the small differences that may become apparent between non-CF individuals and CF-patients it is difficult to base conclusions on a comparison with literature data. An impressive example of the tremendous discrepancies between the pharmacokinetic results in healthy volunteers obtained by different authors is given by *Bergan* et al. (13), *Lode* et al. (14) and *Aronoff* et al. (15) for mezlocillin (Table 1). Whose findings should one use as control-group data for a comparison with one's own group of CF-patients? Any conclusion may be possible, depending on which comparison is being made. Furthermore, since most authors do not give individual data on their subjects, no statistical analysis between the results for normal individuals and CF-patients is possible. The same applies for many other antibiotics. The CF-groups studied were often very inhomogeneous in age (e.g. six to 32 years, see Table 2). We are aware of this problem and realize that control groups in the age range six to 18 years are difficult to recruite, due to ethical and legal problems. The use of very sick children as controls seems to us the least suitable way, scientifically. Children with cancer or having cancer treatment (18) or renal failure (17) will have quite significantly affected pharmacokinetics and thus are not an adequate control group.

Table 1: Total clearance (ml/min) of mezlocillin in healthy volunteers as published by three different authors.

Dose		1 g	3 g	5 g
Bergan et al.	(13)	520.0	–	282.7
Lode et al.	(14)	–	–	113.2
Aronoff et al.	(15)	322.4	251.8	230.3

Table 2: Demographic characterization of the CF-patient populations as studied in three investigations cited frequently.

Compound	Patient population Age (years)	Weight (kg)	Authors
Dicloxacillin	9–20	18.2–55.9	*Jusko* et al. (6)
Ceftazidime	6–32	No data	*Strandvik* et al. (16)
Tobramicin	8–23	No data	*Levy* et al. (17)

Variability of Data for CF-patients Between Different Investigators

As is the case for healthy volunteers, there is also a great variability of data between different investigators for CF-patients. This is evident from the azlocillin and cefsulodin situation. Both agents have significant antipseudomonal activity and have, therefore, been extensively studied for their pharmacokinetics in CF-patients and healthy volunteers. Tables 3 and 4 show the contradictory results and lead to the frustrating situation of not knowing what data to believe and what conclusions to draw when treating a

Infection 15 (1987) Nr. 5

possibly severely sick patient who requires treatment with either agent.

With the cefsulodin data we give an explicit example of all the possible interpretations of published data (Table 4). As has been graphically shown in the table, the reader can arbitrarily select between data and can come to three possible conclusions. As mentioned above, one shortcoming of this comparison is that individual data were not given in the respective papers so that we could not perform statistical tests with the data in Tables 3 and 4. This was also the case for authors using these data for comparison, yet they still drew conclusions on altered pharmacokinetics as found in the paper by *Reed* et al. (25).

Explanations for these discrepancies are still scarce but different populations cannot be the sole explanation. Inadequate assay methods and calibration methods or erroneous pharmacokinetic calculations are certainly more important factors.

Pharmacokinetic Calculations and Pharmacokinetic Concepts

In the pharmacokinetic interpretation itself, authors use pharmacokinetic misconceptions such as clearance being dependent on the volume of distribution (25, 27). Although this is arithmetically true, it has no conceptional or physiological basis (28–31). Also, the modelling of data may often have been inadequate, but since no individual data were given, this is difficult to prove or disprove.

Analysis of Antimicrobials in Biological Specimens

The most modern and specific analysis of antimicrobials should be used for the measurement of antimicrobials in plasma, urine or other biological fluids. High pressure liquid chromatographic analysis of many groups of antibiotics is today considered superior to biological measurement of antibiotics. This is certainly true in the hands of expert investigators, but insufficient chromatographic separation on HPLC may be just as erroneous as non-specific measurement of agents by agar diffusion methods.

Table 3: Pharmacokinetics of azlocillin in CF-patients. Data from three frequently cited papers.

Authors	Dose mg/kg	Total clearance ml/min	Renal clearance ml/min	t 1/2 min
Bergan et al. (19)	100	232.2	162	45
	200	85.0	27.5	58.8
Bosso et al. (20)	58.3	82.9	37.0	79.2
	87.5	81	49.2	71.7
Malmborg et al. (21)	200	n.d.	n.d.	84

n.d. = not determined.

Our Studies

In view of the shortcomings of previous work as mentioned above, our work, included in abstracted form in this pharmacokinetic review, has consequently been performed under conditions which allow more valid conclusions to be drawn.

Control and CF-patient Groups

We only studied CF-patients above the age of at least 16 years. The healthy controls could not be entirely age-matched, but since no differences in the pharmacokinetics have ever been described for healthy volunteers in the age range between 16 and 30, we concluded that our control subjects (age 18 to 25) were adequate.

Study conditions were identical for both groups. Blood sampling and further handling of samples can be extremely critical in pharmacokinetic studies. We therefore performed our studies under the same conditions and at the same time for both groups. The latter measure avoided different stability of samples for either group and thus significantly affected plasma or urine levels.

Identical Chemical Analysis, Quality Control, Pharmacokinetic Calculations and Statistics

Since all analytical work was done at the same time and at one institute, identical conditions applied to all stages of the analyses (chemical analysis and computer analysis).

Table 4: Pharmacokinetics of cefsulodin in healthy volunteers (C) and CF-patients.

Comparison	Population	Comparison	Total clearance (ml/min)	Renal clearance (ml/min)	Authors	
	C	----	128–148	52–60	*Grannemann* et al.	(22)
	C	.....	99	77	*Ahrens*	(23)
	C		181	141	*Arvidsson* et al.	(24)
	CF		117	90	*Reed* et al.	(25)
	CF	.....	178	140	*Arvidsson* et al.	(24)
	CF	----	89	–	*Michalsen* et al.	(26)

———— = Comparison of total clearance with the result: no difference between C and CF;
– – – – – – = Comparison of total clearance with the result: CF-clearance ≪ C-clearance;
. . . . . = Comparison of total clearance with the result: CF-clearance ≫ C-clearance.

Again, in view of the slight differences that may be seen, this was valid background information for our work.

Pharmacokinetics of Antimicrobials in Cystic Fibrosis

Gastrointestinal Function and Drug Absorption

It has been believed for a long time that compounds like vitamins (10) are poorly absorbed in CF.
Guggenbichler et al. (12) seemed to support that view when they showed that the absorption of oral cephalosporins is impaired in CF. *Nahata* et al. (32) and our group were not able to confirm those data (Table 5). We showed that cefadroxil and cefaclor are completely absorbed from the gastrointestinal tract of CF-patients (33–35). This finding may also be of some theoretical interest for the understanding of intestinal transport systems in CF. *Kimura* et al. (36) described a transport system that carries cefadroxil through the epithelia of the gastrointestinal tract. Our findings would have to be interpreted without considering the possibility that this transport system might be affected in CF. Recent data on cloxacillin by *Spino* et al. (37) prove that for another β-lactam the absorption of β-lactam compounds is not affected in CF.
Dickinson et al. (38) showed the influence of pancreatic supplementation on the absorption of chloramphenicol. Although highly speculative at the present time, it is suggested that only absorption processes that require pancreatic or biliary excretory function may be affected in CF.

Renal Function and Pharmacokinetics

Renal function plays a predominant role in the pharmacokinetics of antibiotics since most of them are eliminated via renal transport systems. Renal excretion mechanisms for foreign compounds are often related to kidney function parameters such as glomerular filtration rate or paraamino hippuric acid clearance to calculate the secretory or reabsorptive tubule function for the respective compound.
Conflicting data are available on kidney function in CF. Presently, there is no evidence that CF-patients have a "hyperfunction" of their kidneys as could have been concluded from pharmacokinetic studies (6, 7, 19) as well as from studies on creatinine clearance (6) or inulin clearance (24). Most recent data on the clearance of these endogenous and exogenous compounds (39–41) and those of iothalamate (42) do not support that view. Data that seemed to suggest that there is a decreased tubular secretory capacity for cefsulodin in CF (24) were based on a calculation error as the 1984 Brighton conference on CF showed (the individual data that led to that conclusion were presented for the first time by the authors during that conference [45]; in their original publication [24] only the means were given). An extensive compilation of the available data on kidney function in CF is given in Table 6.

Hepatic Function

It has long been recognized that liver function of CF-patients deteriorates during the progress of the disease and attempts have been made to diagnose early on these changes in the CF-patient (46–48). Changes in liver function do significantly affect the pharmacokinetics and metabolism of foreign compounds. There have been very few antibiotics with significant hepatic metabolism until recently. However, the era of quinolones has already produced several compounds that undergo significant metabolism, such as demethylation and oxidation. There should be some concern about the metabolism of hepatically cleared compounds in CF-patients. No impaired drug metabolism was found for theophylline by *Isles* et al. (49) who instead found increased clearance of theophylline. This would suggest that the metabolic degradation (= methylation) of that compound is increased. That comparison suggests that different pathways of drug metabolism are affected differently in CF.

Weight Correction of Pharmacokinetic Parameters

As has already been mentioned above, increased renal and total clearance have been described as special pharmacokinetic features of antibiotics in CF. In most of these

Table 5: Pharmacokinetics of cephalexin, cefaclor and cefadroxil in CF-patients and healthy volunteers.

	Cephalexin (Data from *Nahata* et al. [32])			Cefaclor (Data from *Sörgel* et al. [33]), Cefadroxil (Data from *Sörgel* et al. [34])			
	CF	CF	C	C	CF	C	CF
Age (years)	9.47 ± 2.24	27.9 ± 5.59	27.9 ± 5.27	23.7 ± 2.9	19.8 ± 3.2	23.7 ± 2.9	19.8 ± 3.2
Weight (kg)	26.5 ± 5.4	68.7 ± 12.2	62.2 ± 4.1	68.8 ± 10.7	49.6 ± 10.9	68.8 ± 10.7	49.6 ± 10.9
C_{max} (mg/l)	25.7			20.4 ± 4.2	21.7 ± 2.7	27.2 ± 2.89	30.4 ± 4.8
t_{max} (h)	–	–	–	0.83 ± 0.26	1.31 ± 0.37*	1.67 ± 0.41	2.00 ± 0.71
AUC (mg, h/l)	8.48	16.6	16.9	30.0 ± 8.6	39.0 ± 4.4*	103.5 ± 11.3	105.5 ± 10.2
CL_{ren} (ml/min)	155	317	–	481.2 ± 176	321.1 ± 38.9*	180.2 ± 19.2	163.0 ± 23.4
$t_{1/2}$ (h)	0.74 ± 0.08	0.97 ± 0.35	1.04 ± 0.18	2.27 ± 2.6	1.36 ± 0.7	1.54 ± 0.19	1.75 ± 0.41

– = no data given;
* = $p < 0.05$.

Table 6: Kidney function in cystic fibrosis and controls.

	Inulin-clearance (ml/min/1.73 m²)	Creatinine-clearance (ml/min/1.73 m²)	Renal blood flow (ml/min/1.73 m²)
Jusko et al [6]	–	CF 196	–
	–	C 127	–
Levy et al. [17]	CF 147.5 ± 29.2*	C 133.8 ± 24.6	–
	C 142.9 ± 33.3*	C 145.8 ± 23.4	–
Yaffe et al. [7]	–	CF 163 ± 38	–
	–	C 171 ± 52	–
Arvidsson et al. [24]	CF 142 ± 38	–	–
	C 102 ± 15	–	–
Marra et al. [40]	CF 142 ± 40	–	–
	C 137 ± 28	–	–
MacDonald et al. [43]	CF 111 ± 26	–	770 ± 140
Aladjem et al. [39]	–	CF 83.8 ± 17.4	–
	–	C 93.3 ± 19.3	–
Robson et al. [41]	CF 120	–	–
Spino et al. [42]	CF 95.8 ± 20.0**	–	499.8 ± 60.2***
	C 98.9 ± 12.9**	–	496.9 ± 102.3***
Berg et al. [44]	CF 127 ± 18	–	616 ± 78+
	C 112 ± 10	–	601 ± 67+
Reed et al. [(25]	–	CF 112.4 ± 24.5	–

* Iothalamate-clearance;
** ^{99m}Tc-DTPA (diethylentriamine-penta-acetic acid) – clearance;
*** ^{125}I-OIH (orthoiodohippurate) – clearance;
\+ PAH – clearance;
C Controls;
CF Cystic fibrosis.

studies total clearance is increased either as a consequence of increased renal clearance or extrarenal clearance. Induction of hepatic drug metabolism by pancreatic enzymes, as suggested by *Spino* et al. (37), is a hypothetical mechanism for the elevation of extrarenal clearance in CF and has no experimental proof yet.

A theoretical consideration which has considerable influence on the calculation and interpretation of pharmacokinetics in CF is the correction of clearance parameters by body weight. Since not yet mentioned in any paper, the physiological basis for doing this needs further discussion. The assumptions that need to be validated are that body size and organ size (liver, kidney) as well as organ size and organ function are correlated. While the first assumption can be accepted with certain limitations, the second does not have much experimental or physiological evidence. A most interesting discussion on that issue is found in a paper by *Falch* (50) who showed that if creatinine clearance is included in the analysis of data to avoid the influence of impaired kidney function there is no evidence that body size is the determining factor of digoxin pharmacokinetics. It is reasonable to believe this because why should the function of an organ depend on body weight e.g. if the subject's weight is in the normal range? Certainly, comparing the clearance of a man weighing 90–100 kg to that of a ten year old CF-child weighing 15 kg some kind of correction of clearance is required. When correcting the clearances of adult CF-patients by weight, however, one would have to assume that organ function in CF-patients does not mature with age but with weight. Most functions of disease-unaffected organs in CF-patients, however, are normal and show the same capacities as those of normal individuals. If clearance values are corrected for weight they consequently falsely mimic hyperfunction of the organs in question. A kidney hyperfunction has thus been found, although the plasma levels from which this has been calculated may have been very similar in both groups. Since the plasma level and not the clearance is the pharmacokinetic parameter in equilibrium with the tissues and the site of infection respectively, there is no reason to give tremendously higher doses of antibiotics.

For further discussion on the weight-correction issue, including matters of volume of distribution, we refer to extensive work by *L. Bauer* et al. (51–53).

Sputum Concentrations

The unresolved question of whether sputum concentrations are a meaningful parameter to evaluate the efficacy of an antibiotic will not be discussed here. A critical comment has to be made on the often used assumption that higher sputum levels are necessary to achieve better effects of antibiotics. There are no data available to prove a relationship between sputum concentrations of an antibiotic and the clinical outcome of antibiotic treatment. *Reed* et al. (54) gave heroic doses of piperacillin (600–900 mg/kg) to CF-patients but did not report any superiority

of those doses over normal doses. *Penketh* et al. (55) and *Cabezudo* et al. (56) demonstrated in their studies that there were patients with no measurable or antimicrobially effective sputum concentrations but good clinical response. In the study by *Cabezudo* et al. (56) doses of cefsulodin between 500 mg/6 hours and 1500 mg/6 hours did not yield a clear dose dependent increase in sputum concentration of cefsulodin. Most recent data on the penetration of anti-*Pseudomonas aeruginosa* quinolones into sputum suggest extremely good penetration of these compounds yielding up to 70% of the plasma concentration in sputum. Still, the clinical outcome from therapy with quinolones does not seem to be any better than that of β-lactams and/or aminoglycosides. Why patients should therefore receive even higher doses of antibiotics lacks experimental proof at the present time and may at some time be shown to be irrational.

Pharmacokinetics of Specific Drugs in CF

In this section the problem of weight corrections will not be specifically discussed since that issue has not been addressed in any of the papers. In addition, since no individual data have been given, a recalculation of data without the weight correction is often impossible.

Gentamicin

This agent has a long and proven role of *P. aeruginosa* treatment in CF and non-CF-patients. The pharmacokinetics in CF are, however, still contradictory. At the present time it is difficult to decide which papers should be used for dosage calculations. From their pharmacokinetic data *Mac Donald* et al. (43) suggest a 60 mg/m^2 dose, while *Bauer* et al. (57) gave dosage recommendations of 2.5 mg/kg/dose respectively. *Bauer* et al. (57) suggest individual dosage adjustment after a few doses as did *Kearns* et al. (27) who disagreed with previous suggestions by *Hendeles* et al. (58) and concluded from their data that the large interpatient variability requires drug monitoring from the first dose on. We agree with the conclusions of *Kearns* et al. (27) that "gentamicin dosing is not yet feasible for a generalized approach" and should rather be individualized. In view of the tremendous difference in total clearance between the data of *Kearns* et al. (27) and *Mac Donald* et al. (43), where the total clearances were 2.51 ± 0.173 and 0.925 ± 0.368 ml/min/kg respectively, it is readily evident that further work is certainly necessary to clarify the obvious discrepancies.

Tobramicin

The controversies for this compound are smaller (57, 59–61), however, there is only one real prospective study that meets some of the requirements for adequate studies as mentioned above. The results of that study suggest a small and statistically significant higher total clearance but identical renal clearance of tobramicin. This is surprising since the mechanism of enhanced elimination of aminoglycosides in CF has always been considered to be of renal origin.

Table 7: Pharmacokinetics of netilmicin.

	Michalsen et al. (26, 62)		*Bosso* et al. (63)$^{++}$
	C	CF	CF
Age (years)	7.0 ± 4.4	7.2 ± 4.8	16 (5–29)
Weight (kg)	24.9 ± 13.3	18.8 ± 7.8	–
Vd_{ss} (l)	–	–	12.4 ± 5.2
Vd_{ss} (l/kg)	–	–	0.38 ± 0.01
Cl_{tot} (ml/min)$^{++}$	52.0	51.3	84.9 ± 38.3
Cl_{tot} (ml/min/kg)$^{++}$	2.08	2.73	2.62 ± 0.18
$t_{1/2}$ (h)	2.29 ± 0.86	1.37 ± 0.27	1.87 ± 0.10
Vd_{β} (l)	9.1 ± 5.8	5.9 ± 3.5	–
Vd_{β} (l/kg)	0.36	0.30	–

$^{+}$ = Controls were not studied;
– = not calculated;
$^{++}$ = S.D. could not be calculated since no individual data were given;
* = Control group used from literature had a Cl_{tot} of 1.42 ml/min/kg and Vd_{ss} of 0.38 l/kg (64, 65).

Netilmicin

Table 7 shows the available results which are self explanatory. Again there is disagreement between different authors. While *Michalsen* et al. (62) conclude from their study that there is no need for higher doses in CF, *Bosso* et al. (63) come to the opposite conclusion since they found a higher total clearance of netilmicin in CF compared to controls. It has to be mentioned, however, that *Michalsen* et al. (62) did study an age matched control group (1.5–12.8 years) and therefore their conclusions are certainly more valid than those of *Bosso* et al. (63) who studied a group of CF-patients very inhomogeneous in age (five to 29 years) and make a comparison with literature data of adults (64, 65).

Azlocillin

We are aware of three pharmacokinetic studies with azlocillin in CF. Due to variable doses studied and the fact that the pharmacokinetics of azlocillin are nonlinear it is most difficult to make valid comparisons. The contradictory results become, however, clearly apparent when the data of *Bergan* et al. (19), *Bosso* et al. (20) and *Malmborg* et al. (21) are directly compared (Table 3). Although *Bosso* et al. (20) studied a lower dose (87.5 mg/kg) than the 100 mg/kg by *Bergan* et al. (19) they still found a dramatically lower total clearance. The renal clearance reported by *Bosso* et al. (20) at roughly similar doses is even less than one third of that described by *Bergan* et al. (19). Half-life also varies considerably between the authors. Azlocillin pharmacokinetics in cystic fibrosis therefore has to be considered unresolved and at the present time

Infection 15 (1987) Nr. 5

no dosage regimen based on pharmacokinetic data can be deducted from the published material.

Piperacillin

Three papers are presently available on the pharmacokinetics of piperacillin in cystic fibrosis (66–68). Enhanced elimination was reported by *Prince* et al. (66) and *Hoogkamp-Korstanje* et al. (67). Our preliminary data (35) again do not support the view of higher clearance in CF when no weight or body surface correction was being made (Cl_{tot} – CF = 151.6±31.1, Cl_{tot} – C = 193.0±31.0). When non-adult patients were studied under drug monitoring conditions (details will be explained in the ceftazidime section below) we did find higher clearances in CF-patients which became particularly prominent when weight or body surface corrections were made. This finding of higher clearance in younger CF-children does not seem to be a special feature in this group of patients since this is also seen in non-CF-children in the prepubertal age (69). That again supports our call for adequately designed studies with age-matched control groups.

Ticarcillin/Clavulanic Acid

This semisynthetic penicillin has properties which make it suitable for use in CF-infections. However, its β-lactamase susceptibility limits its use without a β-lactamase-inhibitor like clavulanic acid. There is only one recent CF-study by *Jacobs* et al. (70) which again demonstrates that the conclusion depends on the comparison being made. At the present it seems prudent to not assume a drastically increased clearance of ticarcillin and clavulanic acid in CF.

Imipenem/Cilastatin

Although there have been several investigations in healthy volunteers as well as in children, there is only one study in CF-patients. It is difficult to decide whether these agents are really excreted more rapidly in CF-patients than in healthy volunteers. *Reed* et al. (71) did not show increased clearances of these two agents in CF-patients, but they still conclude that a 90–100 mg/kg/day dose (divided into four doses) should be administered to achieve serum concentrations above the MIC for *P. aeruginosa* throughout the dosing interval. This is significantly more than those suggested for non-CF-patients (suggested dose for adults 4 × 1000 mg/day). The dose of the two drugs has been arbitrarily selected since "the concentration at the site of infection" is difficult to measure. We do not agree that the serum concentration reflects the active concentration at the site of infection. In addition to arguments used above it is emphasized that no data are available on the extent of penetration of imipenem/cilastatin into sputum of CF-patients and their therapeutic meaning.

Ceftazidime

Of all studies mentioned previously there is only one which meets the requirements we have discussed above (e.g. adequate control group). The results of that study, by *Leeder* et al. (72), are shown in Table 8. When the data are taken as presented (clearance corrected per body weight or body surface), there were statistically significant differences in total and renal clearances between healthy volunteers and CF-patients. Since they show no individual data it cannot be concluded whether the statistical difference still remains when no weight corrections were made. Clearly, the difference becomes smaller when weight corrections are omitted. Several other reports are available but difficult to interpret since control groups were not studied (75–77).

Our investigations with bolus administration of 2 g ceftazidime in adult CF-patients showed that if there is no weight correction of clearance in CF-patients there is no statistically significant difference between healthy volunteers and CF-patients (C = 109.7 ± 27.0, CF = 104.2 ± 48.9).

In addition to the bolus study we performed drug monitoring during ceftazidime therapy. To determine the elimination parameters we infused ceftazidime to steady state concentration and collected blood and urine accordingly. This procedure may be used for establishing the

Table 8: Pharmacokinetics of ceftazidime.

	Leeder et al. (72)		*Sörgel* et al. (35, 73)	
	C	CF	C	CF
Age (year)	21.6 ± 1.9	20.8 ± 4.8		
Weight (kg)	77.0 ± 14.8	55.2 ± 9.1	66.1 ± 5.4	42.9 ± 13.4
Vd_{ss} (l)	15.7⁺	13.1⁺	13.8 ± 2.15	9.6 ± 5.2°
Vd_{ss} (l/kg)	0.197 ± 0.03	0.237 ± 0.03*	0.205	0.211
Cl_{tot} (ml/min)⁺	115⁺	135⁺	109.7 ± 27	104.2 ± 48.9
Cl_{tot} (ml/min/kg)	1.49 ± 0.2	2.45 ± 0.33‡	1.66	2.67°

° = $p < 0.1$;
* = $p < 0.05$;
‡ = $p < 0.001$;
⁺ = calculated from the mean data for Vd_{ss}/kg and weight.

pharmacokinetics of antibiotics with linear pharmacokinetics. The procedure has several advantages: it allows capillary blood samples to be used for the measurement of drug concentrations which are very suitable for individualization of antibiotic therapy and minimum blood requirements in CF. In clinical practice this would mean that the pharmacokinetics may be determined on the first day of treatment by one or two capillary blood samples (minimum requirements for our HPLC-assay 5 µl of blood) and the results will subsequently be used for the calculation of the dosing. Since *Leeder* et al. (72) could demonstrate that multiple dosing does not affect the pharmacokinetics, these clearance estimations of the first day can be used for the whole treatment period. Possibly these data can also be used for following treatment periods and thus may be used to account for intrapatient variability of pharmacokinetics on different exacerbations of the disease.

During such a drug monitoring program we were able to study non-adult CF-patients. The preliminary findings were very similar to those with piperacillin: we found higher clearances with decreasing age if weight corrections were being made. We found no circadian rhythm of ceftazidime plasma concentrations. The sputum levels that we found by HPLC-measurement were also surprisingly constant (1–2 µg/ml). From single dose studies we know that the concentrations reached after bolus doses are not significantly higher.

Fluoroquinolones

The fluoroquinolones are a new group of antibacterials which differ from their congeners nalidixic acid and pipemidic acid in their antimicrobial spectrum and antimicrobial activity (78). The new agents have a broad antimicrobial spectrum with very high activity leading to MIC's in the ng/ml range. Their activity against *P. aeruginosa* makes them potentially important agents in the treatment of *P. aeruginosa* infection of CF-patients. In contrast to the other anti-*Pseudomonas* agents discussed above they can be administered by the oral route which could make them suitable for outpatient treatment (79).

Pharmacokinetic data in CF-patients are particulary important since these agents have side effects – even at normal doses – which do not yet allow treatment of adolescent or younger children (80). High dose treatment as described for aminoglycosides and β-lactams would be a potential hazard for these patients.

We investigated ciprofloxacin and pefloxacin, two new quinolones with slightly different chemical structure but considerably different pharmacokinetic behaviour in healthy volunteers (81–84). Only adult CF-patients participated in our studies.

Ciprofloxacin

We found that ciprofloxacin is equally well absorbed in patients with cystic fibrosis and in healthy controls (Table 9). This is shown by an identical renal excretion of unchanged ciprofloxacin. The comparison of AUC-values for determining bioavailability would not be valid since CL_{tot} has not been determined in CF-patients. In contrast to findings of *Bender* et al. (85) and *Kurz* et al. (86) we found a higher consistency in C_{max} and t_{max} values and the individual plasma curves. There is no evidence from our data of a retardation of the absorption process.

We found identical renal clearances of ciprofloxacin in CF-patients and controls which is in agreement with *Bender* et al.'s (85) data. The half-life in both groups of *Bender* et al. (85) was also identical. Thus decreased extrarenal clearance may be the source of AUC-elevations in CF.

An extremely interesting and well designed study has most recently been presented by *LeBel* et al. (87). These authors studied the pharmacokinetics of ciprofloxacin in two age-matched groups and met most requirements for comparative studies mentioned above. Although they applied a different dose and most likely different batches of tablets compared with ours, there is still much similarity with our data. It is evident from their and our work that

Table 9: Pharmacokinetics of ciprofloxacin in controls (C) and CF-patients. The doses applied were 750 mg (our data) and 500 mg (*LeBel* et al. [87]).

	Our data (from *Sörgel* et al. [88])		*LeBel* et al. (87)	
	C	CF	C	CF
C_{max} (µg/l)	2.34 ± 0.42	3.46 ± 1.26*	3.51 ± 1.33	3.78 ± 0.97
T_{max} (h)	1.12 ± 0.44	1.25 ± 0.38	1.04 ± 0.42	1.72 ± 0.44 **
ka (h^{-1})+	1.71 ± 1.96	1.34 ± 0.79	2.301 ± 0.824	0.862 ± 0.662***
$t_{1/2}$ (h)	4.07 ± 1.14	3.75 ± 1.38	4.87 ± 1.30	3.90 ± 1.71
Cl_{tot}/F (ml/min)	–	–	690.6 ± 297.0	601.3 ± 133.1
Cl_{ren} (ml/min)	265.6 ± 50.3	245.4 ± 96.1	358.4 ± 135.8	319.1 ± 156.9
Vd_{ss} (ml/min/kg)	–	–	3.71 ± 0.96	2.29 ± 0.98

* = $p < 0.05$;
** = $p < 0.01$;
*** = $p < 0.001$;
– = not calculated since F is not known in CF-patients;
+ = using two compartment-model.

Infection 15 (1987) Nr. 5

the peak plasma concentration of ciprofloxacin is higher in CF compared to normal. Unlike previous assumptions on gastrointestinal function there is no evidence of impaired absorption or a significant delay of absorption of ciprofloxacin which is consequently reflected by a smaller absorption constant (ka) in CF-patients. *LeBel* et al. (87) and ourselves (88) also found $t_{1/2}$ slightly longer in controls than in CF, while the renal clearance remained unchanged.
LeBel et al. (87) also studied for the first time the penetration of a compound into blister fluid of CF-patients. Most interestingly, the concentration in that fluid, which represents extracellular or interstitial space in the body, was identical in both groups. The differences in volume of distribution between normal individuals and CF-patients should therefore result from a smaller cell mass in CF-patients into which quinolones can penetrate so easily.

Pefloxacin

This study was the first investigation on the absolute bioavailability of a quinolone in patients with cystic fibrosis (89–90). We clearly demonstrated that pefloxacin has a similar bioavailability in CF-patients and controls (Table 10). This is confirmed by calculation of F by AUC comparison and renal excretion (pefloxacin + metabolites) data. When the variability of F (pefloxacin) from our data is compared to data from *Spino* et al. (37) for cloxacillin (coefficient of variation = 52%) a smaller coefficient of variation in our patients (20–30%) was observed. Whether this is due to greater homogeneity of our patients or whether it is a drug specific effect cannot be decided. In contrast to ciprofloxacin, pefloxacin is a highly metabolized drug with a total clearance of 140 ml/min which was clearly but statistically not significantly decreased ($p = 0.110$) as was the nonrenal clearance ($p = 0.075$). The reduced nonrenal clearance of pefloxacin in CF is also apparent in smaller metabolic rates between metabolites and unchanged compound in urine.
The sputum concentrations of pefloxacin were 60–80% of the plasma levels suggesting a good penetration of pefloxacin into the bronchial system in CF (89).
Summarizing our results with quinolones the most important findings were:
- Higher peak plasma levels and AUC-values of quinolones in CF-patients;
- Normal absorption of quinolones in CF;
- No significant changes in renal clearance of quinolones that would lead to enhanced elimination;
- Smaller total and nonrenal clearance of quinolones in CF;
- Possibly impaired metabolic conversion of quinolones in the liver;
- Smaller volume of distribution of quinolones in CF;
- Very good penetration of quinolones into sputum.

Conclusions

Our literature review and our own findings do not confirm the previous suggestions that the high dose treatment of patients "is rational in view of the pharmacokinetics in these patients" (5). Neither speculations about impaired absorption as seen with vitamins in CF patients nor the "hyperkidney" are features of the CF-patient. To avoid further confusion we would like to point out, however, that our findings were observed in adult CF-patients and cannot readily be applied to younger CF-patients without further experimental proof. The work by *Bergogne-Berezin* (91) and *Grenier* (92) and the netilmicin work by *Michalsen* et al. (26), in which CF-children were compared with adequate age- and sex-matched control groups of non-CF-children show that these findings are probably paralleled by our results in adults. Also, interpatient variability is an important factor in CF-pharmacokinetics. That variability and the slight increases in total clearance as observed by some authors may lead to a 20–30% increase of the antibiotic dose in CF-patients. Drug monitoring whenever possible should be performed in CF-patients. Twofold and threefold doses of antibiotics as previously advocated are not rational on pharmacokinetic grounds.
Another critical comment on the role of pharmacokinetics during dose finding studies in CF seems necessary: although we do not accept high dose treatment on pharmacokinetic grounds we cannot exclude the need for high doses for other, presently unknown, reasons, such as penetration to the site of action, or dose dependent beneficial effects of non-antimicrobial origin. However, for future clinical studies the pharmacokinetic basis is now given and real dose finding studies should be carefully designed on the assumption that the pharmacokinetics is not significantly altered in CF.

Table 10: Pharmacokinetics of pefloxacin in patients with cystic fibrosis following oral and i.v.-dosing with 400 mg pefloxacin mesylate (data from *Sörgel* et al. (35), *Sörgel* et al. [90]).

	C	CF
C_{max} (p.o.)	4.13 ± 0.87 mg/l	4.94 ± 1.74 mg/l
t_{max} (p.o.)	1.6 ± 1.0 h	1.28 ± 0.81 h
AUC (p.o.)	47.7 ± 15.3 mg·h/l	61.8 ± 18.0 mg·h/l
F	1.04 ± 0.21	1.02 ± 0.30
Cl_{tot}	157.26 ± 58.7 ml/min	115.45 ± 42.03 ml/min
Cl_{ren}	11.3 ± 3.28 ml/min	14.75 ± 3.84 ml/min
Vd_{ss} (i.v.)	121.6 ± 44.3 l	101.4 ± 27.8 l
$t_{1/2}$ (p.o.)	10.69 ± 2.18 h	11.35 ± 1.25 h

Acknowledgements

The authors wish to thank *Robert Seelmann*, B.Sc. for excellent analytical assistance and help during the pharmacokinetic evaluations.
Norbert Meister, M.D. and *Nicole Klüting*, M.D. performed the clinical part of most of the studies. Thanks for their warm attitude toward the CF-patients.
The excellent technical and secretarial assistance of Mrs. *Christine Kraus* and Mrs. *Ursula Taube* is greatly appreciated.

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Infection 15 (1987) Nr. 5