Clinical outcome and economic impact of aminoglycoside peak concentrations in febrile immunocompromised patients with hematologic malignancies

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The aim of this study was to investigate the clinical and economic significance of aminoglycoside peak concentrations in febrile neutropenic patients with hematologic malignancies. Sixty-one patients were treated according to protocol II of the Paul-Ehrlich-Gesellschaft: initial application of gentamicin or tobramycin in combination with a cephalosporin or ureidopenicillin and, after 3 days, a potential change of antibiosis to be decided in case of nonresponse. At the same time, samples were collected by an independent controller. We found a significant dependence of clinical outcome on aminoglycoside peak concentrations ($P = 0.004$). Twelve of 17 patients with peak concentrations >4.8 mg/L, but only 13 of 44 patients with concentrations ≤4.8 mg/L, responded to initial therapy. Average infection-related costs per patient with peak values >4.8 mg/L were US$1429, $1790, and $1701 for nursing, diagnostics, and therapeutics, respectively (total $4920). Expenses for patients with peak concentrations ≤4.8 mg/L were 1.8-fold higher (average total $8718). If all 61 patients had achieved peaks >4.8 mg/L, the potential savings would have totalled $167 112. We conclude that neutropenic patients form a target group for successful pharmacokinetic intervention and cost saving.

Rising costs in medical care require enforced efforts for cost reduction without compromising the quality of patient treatment. Several studies have now documented that the appropriate use of therapeutic drug monitoring (TDM), particularly in conjunction with a clinical pharmacokinetic service, is both efficient and cost-effective [1–6]. Further trials are needed, however, to identify drugs and clinical situations for which increased monitoring costs may be justified to both improve the quality of patient care and reduce overall treatment expenditures.

A large and increasing number of patients suffer from malignant diseases. Because of the intensity of antineoplastic chemotherapy, which may induce severe and prolonged myelosuppression, treatment-associated infections are a major cause for therapy failure and death. Overall therapeutic success has therefore become substantially dependent on effective supportive measures [7–10]. A high percentage of these patients present with fever of unknown origin and require intermediate intervention with fixed combinations of antibiotics. The German Paul-Ehrlich-Gesellschaft (PEG) has developed an intervention strategy for the management of infections in neutropenic patients with underlying hematologic malignancies, which has gained international acceptance [9, 11]. The initial antibiotic regimen of the three-phase PEG study protocol II [11] comprises an aminoglycoside in combination with a ureidopenicillin or a third-generation cephalosporin.

In the present study, we investigated febrile neutropenic patients with underlying malignant hematologic disorders, who were treated according to the study protocol II of the German PEG. Aminoglycoside concentrations were adapted according to the pharmacokinetic experience of the responsible clinician, without help from a pharmacokinetic consultant.

The aim of this prospective study was to assess the clinical and economic outcome of these patients with respect to the efficacy of aminoglycoside treatment. Diag-
nostic, therapeutic, and nursing care costs were investigated in relation to aminoglycoside peak concentrations and clinical outcome.

**Patients, Materials, and Methods**

**PATIENTS, STUDY DESIGN, SAMPLING FOR DRUG MONITORING**

Sixty-one consecutive patients with malignant hematologic disorders, who developed fever >38.4 °C during neutropenia (<1000 neutrophils/μL), were recruited into this prospective study. Patients were hospitalized in the Department of Hematology and Oncology of the Georg-August University (Goettingen, Germany). All patients were treated according to protocol II of the German PEG (Fig. 1), with initial application of an aminoglycoside (gentamicin, tobramycin) in combination with a third-generation cephalosporin or a ureidopenicillin. A schematic representation of the study design and the PEG stratification is shown in Fig. 1.

Requests for peak and trough concentrations of aminoglycoside and subsequent dosage adjustments were made by the responsible clinician on the basis of pharmacokinetic and clinical experience (support from a pharmacokinetic consultant was not available). The loading dose recommended by the study protocol was 1.5 mg/kg of body weight.

At the end of day 3, the responsible clinician had to decide whether the initial treatment was to be continued or changed. For the study to reliably judge the therapeutic efficacy of aminoglycoside treatment at the time when the change of the antibiotic regimen was to be decided, serum samples for aminoglycoside monitoring were drawn under strictly standardized conditions by an independent controller (aminoglycoside application: 30 min by infusion pump; aminoglycoside trough sampling: immediately before infusion; aminoglycoside peak sampling: 30 min after the end of infusion). Aminoglycoside concentrations of the samples drawn by the independent controller were not considered for aminoglycoside dosage adjustment and were not reported to the clinician. These additional samples were taken under informed consent of the patients. The study was approved by the local Ethics Committee.

**Stratification of patient groups.** The two patient groups compared with respect to clinical and economic outcome were classified by means of a discriminator, according to aminoglycoside peak concentrations on day 3. The discriminator was calculated by logistic regression analysis under the minimal condition that patients with aminoglycoside peak concentrations above this value should achieve a therapy response probability of >0.6.

**Determination of aminoglycoside concentrations.** Gentamicin and tobramycin concentrations were determined with a fluorescence polarization immunoassay on a TDx/FLx or AxSym analyzer (Abbott Labs.), according to the recommendations of the manufacturer. Analyses were performed within 3 h after sampling.

**Documentation of patient-related data.** The following data were documented: diagnosis of primary disease (type of malignancy); localization and type of infection (if available); microbiological (minimal inhibitory concentration, infectious agent) and histopathological data (if available); x-ray and ultrasound findings; age, sex, and body weight; aminoglycoside dosages and dosage intervals; aminoglycoside concentrations on days 1–3; fever course and time of fever response; change of the antibiotic regimen (phase I → phase II); duration of antibiotic therapy; and patient outcome, including nephro- and ototoxicity criteria.
ECONOMIC CALCULATIONS
Economic calculations were based on the expenses caused by infection. Costs for treatment of the primary malignant disease were not considered. In this economic model, costs were included for diagnostics, therapeutics, and nursing. All costs are expressed in US$.

Diagnostics. 1) Imaging techniques: abdomen ultrasound examination, echocardiography, x-ray exposure, and computer tomography scan of the lung. 2) Microbiology and virology: blood culture, smears, bronchial lavage; identification of infectious agent, microbial sensitivity test, and serological investigations. 3) Aminoglycoside concentrations requested by clinicians. 4) Physician’s examination. Order of imaging techniques, bronchial lavage, and microbiological and virologic diagnostics followed the protocol of the PEG II study, depending on the tentative diagnosis and the therapeutic phase.

Therapeutics. Drugs for antiinfective treatment were considered (antibiotics, antimycotics). Costs of total number of ampules and tablets required (not just the costs of the total dosage administrated) were calculated on the basis of the “Großapotheeken-Einkaufspreise” (prices to be paid by pharmacies of large hospitals in Germany).

Nursing care. Need for care of the patients was routinely documented by the nursing staff for 23 different items—including care of the body, support for controlled evacuation of the bowel and bladder, exercise, bedding, and nutrition of the patients; surveillance; and physician’s examination. Order of imaging techniques, bronchial lavage, and microbiological and virologic diagnostics followed the protocol of the PEG II study, depending on the tentative diagnosis and the therapeutic phase.

Statistics
Logistic and linear regression analyses were performed with aminoglycoside peak concentrations in relation to response to antimicrobial therapy and average total costs, respectively, on an IBM-compatible Pentium computer. Statistical software used was from Statistical Analysis Systems (SAS release 6.12 for Windows; SAS Institute) and Microsoft.

Results
Sixty-one neutropenic patients with fever were recruited to the study. Underlying malignant diseases were acute lymphoblastic leukemia (n = 12), acute myeloid leukemia (n = 25), Hodgkin disease (n = 2), non-Hodgkin lymphoma (n = 19), and myelodysplastic syndrome (n = 3). Further demographic data as well as mean aminoglycoside dosage and mean peak and trough aminoglycoside concentrations on day 3 are given in Table 1.

The patients of this study showed a higher-than-average mean distribution volume of 0.285 L/kg total body weight, but this did not prolong the mean aminoglycoside elimination half-life of 2.2 h.

Fifty patients received gentamicin; 11 were given tobramycin. The loading dose of either drug ranged from 0.9 to 2.2 mg/kg body weight (median 1.5 mg/kg), corresponding to the loading dose recommended by the PEG.

Of the 61 patients, 25 responded to initial therapy of the PEG protocol. One patient died during phase I, and 3 patients during a later therapy phase; all 4 deaths were sepsis-related. Aminoglycoside peak concentrations determined at the end of day 3 by the independent controller are presented in Fig. 2. The results are stratified according to the response to initial therapy. Peak values in the commonly recommended therapeutic range (5.0–10.0 mg/L) were found in only 12 of the 61 patients, and none of the patients had an aminoglycoside peak >7.0 mg/L.

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Table 1. Demographic data, aminoglycoside dosage, and peak and trough concentrations of patients.

<table>
<thead>
<tr>
<th>Aminoglycoside peak concn., mg/L</th>
<th>≤4.8</th>
<th>&gt;4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial plasma creatinine, mg/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46 (20–75)</td>
<td>50 (18–74)</td>
</tr>
<tr>
<td>Initial leukocytes/μL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (6–13)</td>
<td>9 (7–13)</td>
</tr>
<tr>
<td>Initial neutrophils/μL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>250 (&lt;100–1400)</td>
<td>450 (&lt;100–1200)</td>
</tr>
<tr>
<td>Mean daily aminoglycoside dosage, mg/kg body wt.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.34</td>
<td>4.78</td>
</tr>
<tr>
<td>Mean peak concn., mg/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Mean trough concn., mg/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6</td>
<td>0.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data presented as median (range).

<sup>b</sup> On day 3.
Although there was a broad overlap of peak values, as seen in Fig. 2, there was a clear tendency to higher concentrations in those patients who were responders in phase 1 of the PEG protocol.

Logistic regression analysis revealed a highly significant (P = 0.004) concentration dependence of clinical outcome on aminoglycoside peak concentrations.

The intercept of the linearized logistic regression curve (therapy response vs aminoglycoside peaks) was 4.8 mg/L. Patients with aminoglycoside peak concentrations greater than this achieved a therapy response probability of 0.6. Of the 17 patients with aminoglycoside peak concentrations >4.8 mg/L on day 3, 12 (71%) were responders (Table 2). In contrast, only 13 of 44 patients (30%) with concentrations ≤4.8 mg/L showed response to phase 1 of therapy. The response to aminoglycoside peak concentrations stratified according to the type of infection is also shown in Table 2. Because neutropenia (<1000 neutrophils/μL) on day 3 may also influence the clinical outcome, we subsequently tested in a bivariate analysis the significance of aminoglycoside concentrations together with neutropenia on day 3 as independent variables. Aminoglycoside peak concentrations still revealed a highly significant (P = 0.005) positive correlation with clinical outcome; the presence of neutropenia showed a weaker influence (P = 0.04).

Infection-related costs were calculated individually for each patient. Table 3 details the average costs per patient stratified according to an aminoglycoside peak value of 4.8 mg/L on day 3. Average nursing care costs during antibiotic therapy were $750 higher in patients with aminoglycoside peak concentrations ≤4.8 mg/L. The difference in costs increased to $1147 when the length of time from start of antibiotic therapy until discharge from hospital was considered. Average diagnostic costs and infection-related drug costs were also much higher in the patients with inadequate aminoglycoside peak concentrations on day 3. The greatest cost difference of $1570 was related to antiinfective drugs. Average total costs for patients with aminoglycoside peak concentrations ≤4.8 mg/L were ~1.8-fold higher than costs for patients whose concentrations were >4.8 mg/L.

A low, albeit significant (P = 0.03), negative correlation could also be demonstrated between total costs per patient and aminoglycoside peak concentrations on day 3 (Fig. 3). There was a much broader scatter of costs in patients with concentrations ≤4.8 mg/L, compared with those with greater aminoglycoside concentrations.

**Discussion**

Neutropenic patients with underlying malignant hematologic disorders are at high risk for severe infections. Based
on large clinical trials that investigated the empirical antibiotic management of neutropenic patients, the initial treatment with an aminoglycoside combined with a cephalosporin or a penicillin derivative is now widely accepted [7, 9, 11–14].

The aim of the present prospective study was to investigate the influence of the aminoglycoside peak concentrations measured on day 3 of the PEG protocol II [11] on both clinical outcome and infection-related costs. The group of febrile neutropenic patients with underlying malignant hematologic disorders was chosen, because the PEG protocol II offers a clearly defined antibiotic stratification with highly standardized and thus comparable medical decision making for each patient. A further reason for the selection of this patient group was the increasing importance with respect to the growing number of malignant disorders and new therapeutic approaches involving high-dose antineoplastic chemotherapy and prolonged severe neutropenia.

During the past decade, economic evaluation of therapeutic strategies has also been increasingly applied in the field of neutropenia. Many of these studies investigated supportive-care measures such as prophylactic administration of recombinant hematopoietic growth factors [15–18]; only a few studies assessed infection-related costs in febrile neutropenic patients [19–26]. These studies were in part retrospective [19], used cost estimations from expert opinions [21], or focused on selected therapeutic approaches such as outpatient antibiotic treatment of low-risk neutropenic patients [22–26]. Furthermore, the role of drug monitoring and dosage optimization was not evaluated in this setting. Additional detailed studies of infection-related costs are therefore urgently required, and guidelines for performing pharmaco-economic investigations should be followed [27].

To our knowledge, this is the first prospective study in febrile neutropenic patients investigating the impact of aminoglycoside peak concentrations on fever response rates and infection-related costs. The 61 patients included in the present study were treated according to common clinical practice in the three-phase protocol II of PEG (Fig. 1). Physicians’ diagnostic and therapeutic decisions with respect to aminoglycoside dosage adjustment in phase I were not influenced by a pharmacokinetic consultant.

Twenty-five of the 61 patients responded to the phase I regimen of the PEG protocol. According to logistic regression analysis, the correlation between patient outcome and aminoglycoside peak concentration was highly significant ($P = 0.005$); a weaker, but still significant, correlation was found for neutropenia on day 3 ($P = 0.04$).

Comparative studies on the therapeutic efficacy or economic impact of two different drugs allow a clearly defined classification of the patients into two subgroups, depending on the respective therapeutic administered. Classification of patients on the basis of a quantitative variable such as aminoglycoside peak concentrations presents a more intricate question. In the present study a discriminator was calculated under the minimal condition, such that patients with aminoglycoside peak concentration above this value should achieve a therapy response probability of $>0.6$. This minimal condition appears useful, based on the phase I response rates achieved in the previous PEG study [9]. Calculation of the discriminator by logistic regression analysis, i.e., the intercept of the linearized logistic regression curve, resulted in an aminoglycoside peak concentration of 4.8 mg/L, a value close to the commonly accepted lower limit of the therapeutic range for gentamicin and tobramycin.

Classification of the investigated patients according to aminoglycoside peak values of $\leq 4.8$ mg/L and $>4.8$ mg/L, respectively, resulted in clearly different response rates of the two groups, thus reflecting the concentration dependency of aminoglycoside efficacy (Table 2). Thirteen of 44 patients (30%) responded to phase I treatment in the group with aminoglycoside peak concentrations $\leq 4.8$ mg/L. In contrast, there were 12 responders (71%) in the group of 17 patients with aminoglycoside concentrations $>4.8$ mg/L (Fig. 2, Table 2). This doubling of the fever response rate in the latter group confirms the effective impact of aminoglycosides in combination with a potent broad-spectrum antibiotic. The leukocyte, neutrophil, and creatinine values in the patients (Table 1) do not in themselves support a positive bias in favor of a better outcome in the group with aminoglycoside peaks $>4.8$ mg/L. The high percentage of low aminoglycoside peak concentrations may in part result from the higher-than-average distribution volume found in these patients.

Response rates stratified according to the type of infection are given in Table 2. After onset of fever, an initially empirical antibiosis was started in all patients; this could, however, be modified after identification of an infectious agent. In contrast, patients with fever of unknown origin needed further empiric therapy, given a lack of diagnostic results. Fever response in this major patient group increased threefold when aminoglycoside peak concentrations were $>4.8$ mg/L. The impact of efficacious concentrations of aminoglycoside on clinical outcome of febrile neutropenic patients thus confirms previous findings in other patient groups at risk [28–30].

The predominant factors influencing infection-related costs—nursing care, diagnostics, and antibiotic drugs—were specifically assessed (Table 3). For these three items, the average infection-related costs of patients with efficacious aminoglycoside peak concentrations $>4.8$ mg/L were between $1429 and $1790. Patients with inefficient aminoglycoside peak concentrations required additional costs of between $1081 and $1570, with the highest increment of costs being for the antiinfective drugs. Average total costs amounted to $8718 in patients with inefficient aminoglycoside therapy vs only $4920 in the adequately treated patients. Thus, costs for inefficiently treated patients were 1.8-fold higher than for patients whose aminoglycoside peak concentrations exceeded 4.8 mg/L. The correlation between infection-related costs and
aminoglycoside peak concentrations was significant ($P = 0.03$), despite a considerable scatter of costs in the patients with inefficient aminoglycoside concentrations (Fig. 3).

Assuming that all of the patients in the present study, including those with inefficient aminoglycoside treatment, would have achieved aminoglycoside peak concentrations >4.8 mg/L and consequently experienced better aminoglycoside efficacy, we can estimate the potential costs of inefficient treatment as follows. The 44 (of 61) patients whose aminoglycoside treatment was inadequate, with insufficient peak values (Table 2), would require mean additional costs of $3798 per patient (Table 3), representing a total potential additional costs of $167 112. Although these figures may vary between different healthcare systems, they represent a basis for expressing the order of magnitude of infection-related costs.

We conclude that therapeutic peak aminoglycoside concentrations were highly associated with improved phase I fever response in neutropenic patients, such that patients whose peak aminoglycoside concentrations were ≤4.8 mg/L on day 3 averaged total costs per patient ~1.8 fold higher than for efficiently treated patients. Therefore, considerable cost savings may be expected from aminoglycoside drug monitoring and adequate dosage adjustment. The results from the first part of this ongoing study show a major impact of aminoglycoside peak concentrations on clinical and economic outcome of febrile neutropenic patients. Such patients thus form an important target group for a successful pharmacokinetic intervention.

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