Pharmacokinetics and bronchial diffusion of single daily dose amikacin in cystic fibrosis patients

F. Canis\textsuperscript{a}, M. O. Husson\textsuperscript{a,\*}, D. Turck\textsuperscript{b}, P. Vic\textsuperscript{b}, V. Launay\textsuperscript{b}, S. Ategbo\textsuperscript{b}, A. Vincent\textsuperscript{c} and R. J. Courcol\textsuperscript{a}

\textsuperscript{a}Laboratoire de Bactériologie-Hygiène, \textsuperscript{b}Service de Pédiatrie and \textsuperscript{c}Laboratoire de Pharmacologie, Centre Hospitalier Régional et Universitaire, 59037 Lille Cedex, France

A single daily dose of amikacin 35 mg/kg by iv infusion over 30 min in 18 cystic fibrosis patients achieved mean serum peak and trough concentrations of 121.4 mg/L (±37.3) and 0.88 mg/L (±0.62), respectively. Pharmacokinetic parameters and bronchial diffusion of amikacin showed marked inter-patient variability. The highest concentrations in sputum were obtained at 2 h (10.95 ± 7.55 mg/L) and decreased slowly to reach a mean concentration of 2.14 mg/L (range 0.2–3.8 mg/L) just before the following infusion. An increase in the body clearance of amikacin and a decrease in the volume of distribution according to age were observed.

Introduction

Pseudomonas aeruginosa is a common cause of recurrent episodes of pulmonary infections in patients with cystic fibrosis (CF). In these patients, such infections are associated with a poor prognosis and prove to be extremely difficult to eradicate. Among the most potent anti-pseudomonal antibiotics, aminoglycosides in association with \(\beta\)-lactams are often chosen to treat these infections in spite of their toxicity. Once-daily administration of amikacin is now proposed\textsuperscript{1,2} and is at least as efficient as conventional multiple dosing as well as being less toxic.\textsuperscript{2} Pharmacokinetic studies after a single daily dose of amikacin in paediatric CF patients are poorly documented. The purpose of the present study was to investigate the pharmacokinetics of once-daily amikacin in serum and its bronchial diffusion in such CF patients.

Patients and methods

Eighteen CF patients (eight of whom were female) with a mean age of 9.8 years (range 1.7–22.2 years) and a mean body weight of 28.7 kg (10.5–73 kg) were studied. This work was approved by the Lille University Hospital Ethics Committee. Written consent of the patient and/or parents was obtained. Bronchopulmonary infection was defined by increased volume and purulence of sputum, deterioration of clinical condition and/or fever. P. aeruginosa was the predominant pathogen isolated from sputum. Secondary effects of aminoglycoside were evaluated before and after treatment. Cochlear tolerance was assessed by audiometry. Renal tolerance was monitored using parameters such as 24 h proteinuria with electrophoresis, lysozymuria, \(\beta\)-microglobulinuria and creatinine clearance.

Amikacin 35 mg/kg/day was administered by iv infusion over 30 min. Ceftazidime or imipenem was administered thrice daily at a dosage of 200 mg/kg/day. Treatment was given for 14 days. None of these drugs was known to have a pharmacokinetic interaction with amikacin. Venous blood and sputum samples were collected immediately before and at 0.5, 1, 2, 3, 4, 6, 12, and 24 h after the beginning of the infusion. Sputum samples were obtained from the lower respiratory tract by physiotherapy and the volume of expectorate was recorded. A II these clinical specimens were immediately analysed or stored at \(-80^\circ\text{C}\) until analysis. Sputa were liquefied using a saline solution containing the mucolytic agent N-acetyl-L-cysteine with a contact time of 18 h at 4°C. Serum and sputum concentrations were studied on the first day of treatment. On day 14, only sera were analysed because no sputa were collected after antibiotic administration ceased. Serum and sputum concentrations of amikacin were measured by fluorescence polarization immunoassay (TDx system, Abbott Laboratories, Chicago, MI, USA). Day-to-day

\*Corresponding author.
reproducibility assays (10 consecutive tests for each concentration) were 4.2, 4.3 and 5.3% for concentrations of 3 mg/L, 15 mg/L and 31.5 mg/L, respectively. Controls of amikacin concentration in sputum using samples free of drugs and supplemented with antibiotic (2 mg/L or 5 mg/L) were included. None of the coefficients of variation for these controls exceeded 10%. The lower limit of sensitivity of this method was 0.2 mg/L. Pharmacokinetic studies of aminoglycosides have demonstrated that they required a two-compartment pharmacokinetic open model. The pharmacokinetic parameters determined for each patient were peak and trough concentrations, serum half-lives ($t_{1/2a}$, $t_{1/2b}$), total volume of distribution (VD), area under curve (AUC) and amikacin body clearance (Cl).  

Statistical analysis was carried out using Pearson’s correlation coefficient; $P$ values $<0.05$ were considered significant.

Results and discussion

Amikacin peak serum concentrations were high, ranging between 42.7 and 176 mg/L with a mean (±s.d.) of 121.4 mg/L (±37.5). The trough concentrations ranged between 0.2 and 1.9 mg/L (0.88 ± 0.62 mg/L). These results obtained in CF patients receiving a once-daily dose of amikacin 35 mg/kg showed a rapid elimination of aminoglycoside. No accumulation of amikacin was observed between the first and the fourteenth day of treatment (Figure 1). Laboratory tests and audiometry showed no evidence of nephro- or oto-toxicity. Pharmacokinetic parameters demonstrated important individual variations. The a and b half-lives varied from 0.65 to 1.92 h and from 3.15 to 16.57 h, respectively. There were no significant differences between pharmacokinetic parameters on day 1 versus day 14. Values were generally higher than those reported by Kafetzis et al. in 10 children with severe Gram-negative infections given a single daily dose of amikacin 20 mg/kg. The VD was high, ranging between 0.5 and 3.77 L/kg with a mean of 1.93 L/kg (±1.94); body clearance was between 1.58 and 7.33 L/h (4.05 ± 1.81 L/kg). Vogelstein et al., comparing pharmacokinetics in CF and non-CF children after four daily doses of amikacin, observed that renal and total clearances were significantly greater in CF children. Similar results were found for tobramycin in CF patients. We observed that amikacin body clearances were lower for younger children, while VDs were higher for these subjects. Correlations between age and clearance ($r = 0.85$; $P < 0.01$) and between age and VD ($r = -0.57$; $P < 0.05$) were statistically significant. These observations may reflect either an increase in the lean body mass to total body weight ratio, as a result of decreased fat absorption, or an increased extra-renal clearance or a large volume of sputa, so increasing the apparent VD, as described elsewhere.

It is possible that if older patients were infected for longer, the VD might reflect the degree of bronchial sepsis. Concentrations of amikacin in sputum were studied for 13 patients on day 1 (Figure 2). There was marked inter-patient variability; amikacin sputum concentrations ranged from 5.1 to 19.9 mg/L at 1 h. The highest concentrations were obtained at 2 h (mean 10.9 ± 7.5 mg/L). Sputum concentrations remained above 8 mg/L at 4 h after infusion, then slowly decreased to reach a trough concentration ranging between 0.2 and 3.8 mg/L. If we consider the post-antibiotic effect of amikacin, described by Hanberger, inhibition of growth of P. aeruginosa might occur at relatively low amikacin concentrations. Sputum concentrations of amikacin were higher than those described by Mombelli et al. who studied a dose of 7–12 mg/kg tds. Higher amikacin concentrations were reported by Autret et al. who observed a mean concentration of 5.4 mg/L at 1–2 h after a daily dose of amikacin 15 mg/kg. From our results, concentrations of antibiotic achieved in the sputum appeared to be highly correlated with the peak serum concentration. In conclusion, after a single daily administration of iv amikacin 35 mg/kg in CF patients, therapeutic antibiotic concentrations were...
Amikacin treatment of CF patients

achieved in both serum and sputum, without evidence of toxicity.

Acknowledgements

We thank the nursing staff for their cooperation, Charlotte Buisine for her dedication to the cystic fibrosis patients, and Beatrice Adriansen and Agnès Perus for their excellent technical assistance. This project was funded in part by a grant from the French Ministry of Health (Clinical Research Program).

References


Received 16 April 1996; returned 27 June 1996; revised 23 July 1996; accepted 11 September 1996