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Short communication

Active pulmonary tuberculosis: Role for amikacin in early treatment

Tuberculose pulmonaire active : rôle de l'amikacine dans le traitement initial de la maladie

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Abstract

Objective. – To evaluate the efficacy of amikacin on sputum conversion during initial sputum smear positive tuberculosis treatment.

Material and methods. – Single-center observational cohort study (2012–2013) evaluating time to sputum smear conversion with standard treatment (ST) versus standard treatment + amikacin (IV 15 mg/kg/day) for seven days (STamK).

Results. – Forty-five patients were included. Median time to smear negative samples was 26.5 days (14–56) for the 30 (66.7%) patients included in the ST group and 48 days (19.5–69.5) for the 15 patients (33.3%) included in the STamK group ($P = 0.76$). Time to negative culture was only known for 27 patients (61.4%): 47.5 days (26–58) for 18 patients in the ST group and 40 days (14–77) for nine patients in the STamK group.

Conclusion. – Despite our small sample size, the addition of amikacin in active tuberculosis treatment did not seem to impact time to smear conversion or period of contagiousness.
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Keywords: Tuberculosis; Isolation; Amikacin

Résumé

Objectif. – Évaluer l'efficacité de l'amikacine sur la conversion des cultures durant le traitement initial des tuberculoses bacillifères.

Matériel et méthodes. – Étude monocentrique de cohorte observationnelle (2012–2013) visant à évaluer le délai de négativation des crachats entre traitement classique (TTBc) et traitement classique plus amikacine (15 mg/kg/j IV) pendant sept jours (TTBamK).

Résultats. – Quarante-cinq patients inclus : 30 (66,7 %) dans le groupe TTBc et 15 (33,3 %) dans le groupe TTBamK. Les délais médians de négativation de l'examen microscopique des crachats étaient de 26,5 jours (14–56) et 48 jours (19,5–69,5) respectivement ($p = 0,76$). Le délai de négativation des cultures n'était connu que pour 27 patients (61,4 %) : 47,5 jours (26–58) pour les 18 patients du groupe TTBc et 40 (14–77) pour les neuf patients du groupe TTBamK.

Conclusion. – Malgré le faible nombre de patients de notre étude, l'amikacine ne semble pas avoir d'impact sur la durée de la contagiosité.
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Mots clés : Tuberculose ; Isolement ; Amikacine

1. Introduction

Tuberculosis (TB) remains a public health problem with 9 million case patients and 1.5 million deaths reported in 2013 across the world [1]. A total of 4934 TB case patients were reported in France in 2013, with an incidence of 7.5/100,000 inhabitants [2]: 3579 (72.5%) were pulmonary TB case patients [2]. Sputum smear positive tuberculosis requires respiratory isolation which is often prolonged and quite restrictive for patients. It is also associated with high costs for the healthcare system. Many physicians keep patients in isolation rooms for as long as the sputum smears remain positive. Time to smear negativity is often long, even in the absence of resistance of the bacterial strain [3]. With appropriate anti-tuberculosis

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treatment, 85% of patients are likely to achieve sputum smear conversion within two months [4]. Few studies have investigated the therapeutic means to reduce time to smear and culture conversion from patients presenting with active tuberculosis [5–8]. Despite multiple studies demonstrating high levels of rapid bactericidal activity of amikacin in pulmonary tuberculosis, this drug is only used with caution in TB second-line regimens because of renal and auditory toxicity associated with prolonged use [4,9–11]. The main objective of our study was to evaluate the effects of adding amikacin to conventional therapy in the early treatment of active pulmonary tuberculosis to reduce time to sputum smear negativity.

2. Material and methods

We conducted a single-center observational cohort study from February 2009 to November 2013 and included all consenting patients aged above 18 years and diagnosed with active pulmonary tuberculosis susceptible to the four standard treatment drugs. Patients presenting with renal insufficiency (creatinine clearance < 90 mL/min as estimated by the MDRD equation) or with HIV co-infection were excluded from the study. All patients were treated with the standard anti-tuberculosis therapy (isoniazid 5 mg/kg/day, rifampicin 10 mg/kg/day, ethambutol 15 mg/kg/day, pyrazinamide 20–30 mg/kg/day). For patients diagnosed from April 2012 onwards, IV amikacin was added during the first seven days of treatment. The primary and secondary endpoints were, respectively, time to smear and culture conversion of sputum or gastric aspirate samples. These samples were collected on days 7, 8, and 9 following the initiation of anti-tuberculosis treatment, and then for three days every two weeks until three consecutive sputum smear negative samples were obtained. Plasma amikacin concentrations were measured to establish baseline and peak values at the start of treatment. Target concentrations were 20–40 mg/L at peak and < 5 mg/L at baseline. Patients did not undergo audiogram as the risk of ototoxicity is low when receiving < 7 days of aminoglycosides. Times to sputum smear conversion by direct examination were compared between patients receiving amikacin and those only receiving the standard anti-tuberculosis treatment. Fisher's exact test was used to compare proportions of categorical variables and a non-parametric test was used to compare medians of continuous variables. Statistical significance was set at $P < 0.05$. Survival analysis was carried out with Kaplan–Meyer curves and a log-rank test. All statistical analyses were performed with Stata 12®.

3. Results

We included 45 patients: 30 (66.7%) in the standard treatment group (ST group) and 15 (33.3%) in the standard treatment + amikacin group (STamK). The male to female ratio was 5.3. There was no significant difference between the two groups, notably in terms of age, sex, and tobacco use (Table 1). Cough and sputum were present in 41 (91.1%) and 30 (66.7%) patients respectively, with no significant difference between the two groups ($P = 0.29$ and $P = 1$, respectively).

Table 1
Descriptive characteristics of the population (number of patients and percentage or median and interquartile range).
Caractéristiques descriptives des patients (nombre de patients et pourcentage ou médiane et intervalle interquartile).

Characteristics	Standard treatment group ($n = 30$)	Standard treatment + amikacin group ($n = 15$)	P[a]
Age	42.65 (36.3–51.5)	34.2 (29.3–48.8)	0.19
Male patients	23 (76.7)	14 (93.3)	0.24
Immunosuppression	1 (3.3)	0 (0)	1
Sputum production	20 (66.7)	10 (66.7)	1
Cough	25 (86.2)	15 (100)	0.28
Radiological pulmonary cavity	28 (93.3)	14 (93.3)	1
Tobacco use	10 (34.5)	7 (46.7)	0.52
Time to sputum smear negativity	26.5 (14–56)	48 (19.5–69.5)	0.51
Time to culture negativity[b]	47.5 (26.3–57.5)	40 (18–59)	0.9

[a] The comparison between the two treatment groups was done using Fisher's exact test.
[b] 18 patients (60%) in the standard treatment group and nine patients (60%) in the standard treatment + amikacin group.

Most patients ($n = 42$, 93.3%) had radiological evidence of a pulmonary cavity. There was no difference in the initial bacillary load between the two groups ($P = 0.58$). Median times to smear negative samples for the ST and STamK groups were 26.5 days (14–56) and 48 days (19.5–69.5), respectively. This result was not statistically significant ($P = 0.76$). The log-rank test did not show significant difference between the groups in terms of time to sputum smear conversion ($P = 0.37$). Time to negative cultures was only known for 27 patients (61.4%), whose last culture of smear samples were negative. Median values were 47.5 days for the 18 patients in the ST group and 40 days for the nine patients in the STamK group. There was no significant difference between these two groups ($P = 0.78$). Seventeen other patients still had positive cultures when their sputum samples tested negative so no further sputum culture was collected. No amikacin-related side effect was reported, including symptomatic ototoxicity and renal toxicity.

4. Discussion

Most patients presenting with drug-susceptible active pulmonary TB achieve smear conversion during the first two months of treatment [4,12]. Minimizing hospital stay is important due to high hospitalization costs, and prolonged respiratory isolation is often difficult in terms of ward organization as well as for the patients themselves. Prolonged stays in infectious disease wards also increase the risk of nosocomial infections, particularly for immunocompromised patients. New therapeutic advances are now crucial to try and identify a treatment that could decrease time to smear conversion and hospital stay. The authors of numerous studies have shown that amikacin is associated with a good bactericidal activity against *Mycobacterium tuberculosis*. Amongst aminoglycosides, amikacin is also associated with the best in vitro activity [13,14]. Sacks et al.

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