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Stability of amoxicillin in portable pumps is drug concentration dependent

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Continuous amoxicillin infusion for deep infection's intravenous treatment is performed using elastomeric portable pumps carried under clothing and requires high doses of antibiotic. Therefore, we evaluated the stability of amoxicillin in those medical devices, with particular focus on both drug concentration and storage temperature. Stability of 20, 40, and 60 g/L amoxicillin solutions in 300 mL portable pumps stored at 20 or 35 °C was studied by visual examination and drug concentration measurements at T0; T0 + 12 h; T0 + 24 h and; T0 + 48 h. Twenty and 40 g/L amoxicillin solutions were stable over 48 h, with a degradation rate that never exceeded 12% at T0 + 24 h, and 18% at T 0 + 48 h. However, the 60 g/L amoxicillin solution degradation rate was significant ($p < 0.05$, versus C_1 and C_2) at T0 + 24 h: 24.5 and 26.9% at 20 and 35 °C, respectively. This degradation process was amplified at T0 + 48 h, with degradation rates of 37 and 42% at 20 and 35 °C, respectively. Stability of amoxicillin in pump is guarantied over 48 h up to concentrations of 40 g/L. At 60 g/L major degradation of the antibiotic was observed.

Antimicrobial treatment of deep infections like bacterial endocarditis (BE), a disease associated with high morbidity and mortality (Chopra and Kaatz 2010), requires regimens based on i.v. antibiotic therapy for as long as 6 weeks, to control the infection (Baddour et al. 2005). Thereby, after initial treatment, ambulatory care may be performed with a continuous infusion system like a portable pump. The antibiotic widely used to treat or prevent endocarditis remains amoxicillin. The minimum bactericidal concentration of amoxicillin greatly exceeds the minimum inhibitory concentration (MIC) (usually by > 32-fold) and high doses of antibiotic, over 12 g per day, are required to achieve a constant bactericidal activity (Tattevin et al. 2005). To date, published data related to amoxicillin stability in an elastomeric infusor are lacking. Therefore, the purpose of this study was to assess, in real conditions, the physio-chemical stability of amoxicillin solutions packaged in elastomeric pumps at concentrations used in BE patients.

No precipitate or colour changes in amoxicillin solutions were noticed over the study. Antibiotic concentrations were determined, and the results are illustrated as residual concentration rates in the Figure 1. At T0 + 12 h, degradation rate of amoxicillin remained under 10% for C_1 and C_2, whatever the storage temperature, whereas C_3 groups showed a higher but not statistically significant degradation rate versus C_1 and C_2: 14 and 16% at 20 and 35 °C, respectively. At T 0 + 24 h, C_1 and C_2 solutions appeared to be quite stable since their degradation rates never exceeded 12%, with residual concentration rates not significantly different to measurements at T0 + 12 h. However, the highest tested concentration C_3 reached significant ($p < 0.05$) degradation rates of 24.5 and 26.9% at 20 and 35 °C, respectively. This degradation process appeared to be maximal at T0 + 48 h with C_3 concentration groups reaching significant ($p < 0.05$) degradation rates of 37 and 42% at 20 and 35 °C, respectively. Furthermore, it is noteworthy that storage temperature did not influence the degradation rate in a statistically significant way, whatever the concentration.

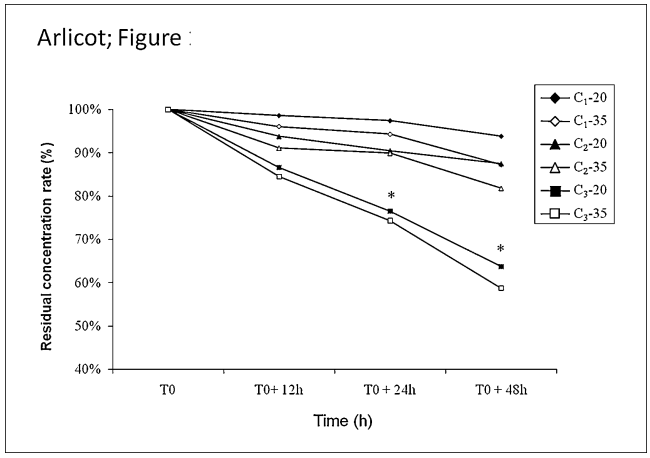

Fig. 1: Residual concentration rates of amoxicillin in portable pump maintained at 20 ± 1 and 35 ± 1 °C over 48 h at the concentrations tested C_1 (20 g/L; 20 °C: ♦; 35 °C: ◊), C_2 (40 g/L; 20 °C: ▲; 35 °C: Δ) and C_3 (60 g/L; 20 °C: ■; 35 °C:). All values are means ± standard deviation (SD) of 2 repeated measurements for each pump. * $p < 0.05$ between C_3 and both C_1 and C_2 measured at the same time point, Student *t* test.

Pharmacodynamic data are in favour of administration by continuous infusion of antibiotics like amoxicillin, because of greater achievable time above MIC. Recent studies support that these advantages of continuous infusion over intermittent administration improve clinical outcomes, especially regarding BE, and that continuous infusion is a safe and effective delivery method in carefully selected BE patients (Amodeo et al. 2009). However, efficiency and safety of continuous antibiotic administration require the drug to remain stable all over the duration of the infusion. Since stability of amoxicillin in aqueous solution can be influenced by many parameters (drug concentration; storage temperature; vehicle (sterile water, dextrose 5% or saline); medical infusion device), it must be proved by physico-chemical studies that mimic real conditions that drug bioavailability is not compromised all over the infusion time. Most of the studies with beta-lactams in infusors have been performed over 24 h at a maximum storage temperature of 25 °C (Viaene et al. 2002). We considered in the present study stability of amoxicillin at 20 and 35 °C - the mean temperature measured into pumps maintained under real conditions of use (Arlicot et al. 2007). The stability of amoxicillin from 10 to 50 g/L has already been evaluated at 25 °C particularly in dextrose 5% and saline (Cook et al. 1982). Stabilities in saline were markedly superior to those in dextrose over 24 h and the authors report a potential correlation between antibiotic concentration and degradation rate. However, these data are not predictive of amoxicillin stability when exposed to higher temperature and packaged in an elastomeric pump.

According to our results, the stability of amoxicillin over a 24-hour period in an elastomeric pump is insured for a concentration range from 20 to 40 g/L, but is compromised if the infusion is prolonged beyond 24 h. Moreover, we observed that 60 g/L amoxicillin solutions exhibited ≈25% losses at T0 + 24 h, reaching ≈40 % degradation after 48 h. Therefore, the stability of amoxicillin in a portable infusor appeared to be tightly linked to drug concentration, and prescribers must be aware that stability of high concentration amoxicillin (> 40 g/L) solution is only insured up to 12 hours continuous infusion.

Injectable drug stability is only ensured under documented validated conditions. Our results support a pharmacologically safe approach of amoxicillin administration through an elastomeric portable infusor (Muller and Haker 2003), and provide guidelines to optimize the safety and efficacy of treatment for patients with deep infection.

Experimental

Lyophilized drugs were obtained through a hospital pharmacy as brand name product from the same lot: Clamoxyl™ (GlaxoSmithKline, Heppignies, Belgium). Stability of amoxicillin was analyzed in a 300 mL elastomeric infusion system (Baxter Healthcare Corporation, Deerfield, ILL, USA) at 3 concentrations: C_1 (50% C_2), C_2 (mean concentration derived from therapeutic protocols for BE patients) and C_3 (150% C_2), corresponding to 20, 40 and 60 g/L, respectively. The study was performed at 20 ± 1 °C and 35 ± 1 °C in monitored incubator Innovens™ (Thermo-electron Corporation, Milford, MA, USA). The 35 °C storage temperature matches with the average temperature measured in the pump reservoir in real conditions (Arlicot et al. 2007). Twenty-four elastomeric pumps were used (n = 4 per group). Infusors were filled aseptically with amoxicillin diluted in saline (CDM Lavoisier, Paris, France) to the right concentration, then immediately stored in obscurity at 20 ± 1 °C or 35 ± 1 °C and maintained under those conditions for 48 h. Stability parameters were visual aspect - aiming to detect particles, precipitate, colour change - and drug residual concentration, all controlled at T0 (infusors filling up time point), T0 + 12 h, T0 + 24 h and T0 + 48 h. Antibiotic concentration measurements were performed at room temperature by a Multispec™ spectrophotometer (Microdom, Taverny, France) coupling a Fourier Transform Infrared and UV/Visible spectrophotometers. The spectral data were acquired simultaneously with both optical benches and processed with Multispec™ Analysis software. A calibration curve was established in the amoxicillin concentration range from 7.5 to 75 g/L. An a Aliquot (1.2 mL) of each antibiotic solution from the elastomeric pumps was injected by the autosampler followed by a IR/UV detector adjusted at the suitable analytical wavelength (between 258 and 274 nm). All reagents for spectrophotometry analysis were purchased from Microdom. Assays showed a range of linearity with a correlation coefficient $r^2 > 0.999$. Absorbance was performed in duplicate for all samples for repeatability testing. Data are presented as mean ± SD. Significance was set at $p < 0.05$. Statistics included analysis of variance (ANOVA) followed by Student's test for drug concentration measurement. Correlation between absorbance and drug concentrations was assessed using the Spearman correlation coefficient.

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