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Antibiotic stability related to temperature variations in elastomeric pumps used for outpatient parenteral antimicrobial therapy (OPAT)

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Background: Elastomeric pumps can be used for the continuous administration of antimicrobials in the outpatient setting. A potentially limiting factor in their use is the stability of antimicrobials.

Objectives: To investigate under real-life conditions the temperature variations of antibiotic solutions contained in elastomeric pumps, and to examine under such conditions the stability of five antibiotics.

Methods: Healthy volunteers carried the elastomeric pumps in carry pouches during their daily activities. A thermologger measured the temperatures every 15 min over 24 h. Antibiotic concentrations were measured by HPLC coupled to tandem MS.

Results: During daytime, the temperature of solutions in the pumps increased steadily, warming to >30°C. During the night, when the pumps were kept attached to the waist, the temperatures reached up to 33°C. The use of white carry pouches avoided excessive temperature increases. Over seven experiments, cefazolin, cefepime, piperacillin and tazobactam were found to be stable over 24 h. Flucloxacillin showed a mean decrease in concentration of 11% ($P = 0.001$).

Conclusions: Real-life situations can cause significant temperature rises in elastomeric pumps, thereby potentially increasing the risk of antibiotic degradation. Patients should be instructed to avoid situations causing excessive temperature increases. Despite these temperature variations, cefazolin, cefepime, piperacillin and tazobactam were found to be stable over 24 h. A moderate degradation was noticed for flucloxacillin, albeit most probably not to an extent that might impair anti-infective efficacy.

Introduction

When considering outpatient parenteral antimicrobial therapy (OPAT) for a patient, selection of a suitable antibiotic should remain guided by the usual criteria of anti-infective therapy (the susceptibility of the isolated microorganism, severity and site of infection) rather than by the availability of some antibiotic that would just be easier to use.[1,2] In this context, elastomeric pumps have proved to be useful and at the OPAT Unit of the University Hospital of Lausanne, Switzerland, elastomeric pumps for continuous antimicrobial infusions are used in more than one-third of patients.[3]

A few practical contingencies may limit the generalized use of continuous infusions with elastomeric pumps. A critical concern is that the stability of the antimicrobials in real-life conditions is poorly defined. An excessive increase in temperature may accelerate drug degradation and might even yield toxic waste products.[4]

At present, the vast majority of published antimicrobial stability data emanate from the manufacturers of elastomeric pumps. According to these sources, the maximal recommended duration of infusion is based on experiments performed under laboratory conditions, whereby antibiotic solutions are exposed to constant temperatures of −5, 5 and 25°C.[4] Only two small studies have explored antibiotic solution stability at a higher temperature of up to 35°C.[5,6]

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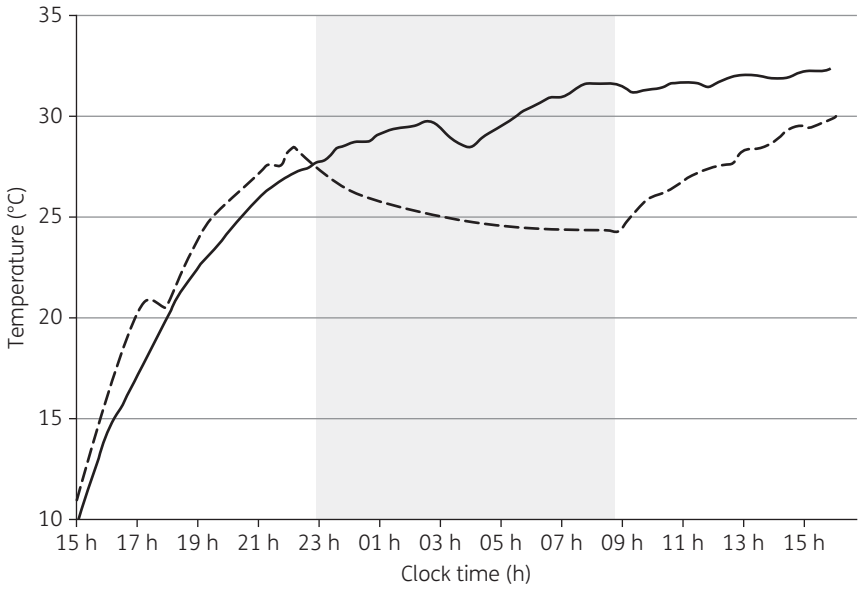

Figure 1. Change in temperature in two elastomeric pumps worn by the same volunteer, one carried attached around the waist (continuous line) and one detached (dashed line) during the night (shaded area).

The aims of this study were to investigate the temperature changes within elastomeric pumps during daily activities of subjects, and to determine the stability under real-life conditions of some antimicrobials frequently used in elastomeric pumps.

Methods

The experiments exploring the temperatures of the solutions in the pumps were carried out in Lausanne, Switzerland, between July 2014 and February 2015. The external temperatures varied between 4 and 27°C during July and between −1 and 12°C during February. Each experiment was repeated three times. Easypump LT-270-24® elastomeric pumps (B. Braun Medical Inc., Melsungen, Germany) were used.

The temperature of the solutions in the pumps was measured every 15 min over 24 h using a temperature logger (LogTag TREX-8, LogTag Recorders, Auckland, New Zealand) equipped with an external temperature sensor (ST100J-15), which was inserted into the hollow cylinder forming the solid base of the Easypump®. In preliminary experiments this set-up was shown to record temperatures that were very close to the real temperature of the solution in the pumps.

The antimicrobial drugs and drug concentrations tested in our study were as follows: flucloxacillin, 33 g/L; cefazolin, 25 g/L; cefepime, 12.5 g/L; piperacillin, 50 g/L; and tazobactam, 6.25 g/L. These concentrations correspond to the following 24 h doses when infused in an elastomeric pump filled with 240 mL of solution and running at 10 mL/h: flucloxacillin, 8 g; cefazolin, 6 g; cefepime, 3 g; piperacillin, 12 g; and tazobactam, 1.5 g. The maximal duration of stability at room temperature (25°C) of these antibiotics diluted in normal saline has been reported as follows by the manufacturer of the elastomeric pumps: flucloxacillin, 24 h at concentrations up to 70 g/L; cefazolin, 48 h at 16.7 g/L; cefepime, 24 h at 20 g/L; piperacillin, 24 h at 80 g/L; and tazobactam, 24 h at 10 g/L.[7]

The antimicrobial drug stability experiments were carried out under real-life conditions that would cause the smallest temperature variations as identified by the above-described experiments. The volunteers were asked to collect 5 mL aliquot samples from the elastomeric pump at the 0, 12 and 24 h timepoints, and to keep these samples stored at 4°C before bringing them for storage at −80°C at the laboratory prior to analysis. For each antimicrobial drug, the experiment was performed on seven different occasions. Antimicrobial drug concentrations were measured by a validated LC–MS/MS method using stable isotopically labelled internal standards and matrix-matched calibration samples. The log-transformed concentration results were analysed with a multilevel linear model; if their slope over time differed significantly from zero, it was transformed back and expressed as a half-life with the 95% CI.

Results

Temperature variations over 24 h in real-life situations

First, we evaluated the time course of temperature of the antibiotic solution during the night when the elastomeric pumps were carried around the subject's waist (continuous curve) versus kept beside the head, outside of the blankets (dashed curve) (Figure 1). The mean temperatures over 24 h derived for these situations were 30.9°C (SD 0.9°C) and 26.2°C (SD 1.0°C), respectively. When the pumps were maintained under the blankets during the night, the temperature of solution increased by 2.6°C (SD 1.4°C) over 6 h, whereas the temperatures decreased by 2.8°C (SD 2.9°C) over 6 h when the pumps were kept outside of the blankets.

Secondly, direct exposure to sun during a summer day led to the following temperature increases: in white carry pouches, the temperature of the solution increased by up to 5.3°C/h during the first few hours of sunlight exposure, reaching a maximum of 38.8°C, while in black pouches the temperature increased by up to 8.3°C/h, reaching 45.4°C.

Thirdly, the usefulness of isothermal carry pouches was investigated. The volunteers simultaneously carried elastomeric pumps placed in a normal carry pouch and an isothermal carry pouch. The type of pouch modified neither the average temperature (26.2°C, SD 3.3°C versus 25.9°C, SD 3.0°C, respectively, $P = 0.60$) nor the

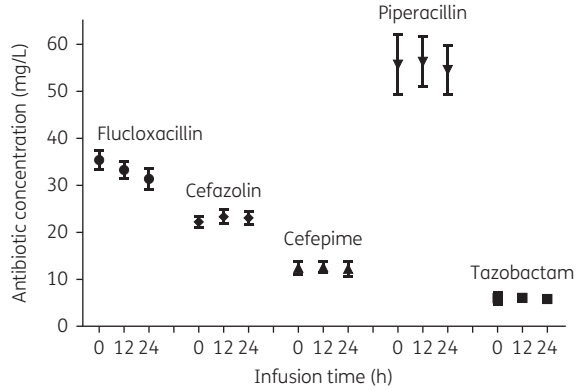

Figure 2. Degradation of antibiotics in elastomeric pumps sampled at 0, 12 and 24 h under real-life conditions expressed as mean concentration and standard deviation.

number of measurements >25°C (60% versus 56.9%, respectively, $P = 0.45$). However, the curves suggest that the isothermal pouch added some caloric inertia to the system.

Antimicrobial degradation

Figure 2 shows the time course of antibiotic concentrations measured at 0, 12 and 24 h in elastomeric pumps. Cefazolin, cefepime, piperacillin and tazobactam were found to be stable over 24 h, with mean concentration changes after 24 h of +4%, −4%, −2% and −2%, respectively. Flucloxacillin, however, showed a mean decrease in concentration of 11% after 24 h. The corresponding slope over time was significantly negative, indicating a degradation half-life of 137 h (95% CI 93–259 h, $P = 0.001$). On this basis, the relative loss over 24 h was estimated to be 11% (95% CI 6%–16%) for flucloxacillin.

Even though elastomeric pumps were supposedly filled with antibiotics at the same concentrations, significant inter-preparation variability was found in these 0 h concentrations, with coefficients of variation of 6.0%, 5.1%, 11.6%, 12.3% and 23.3% for flucloxacillin, cefazolin, cefepime, piperacillin and tazobactam, respectively. Piperacillin and tazobactam, formulated in a fixed combination, were strongly correlated among solutions prepared from a single drug batch ($r^2 = 0.98$), suggesting that the observed variability is explained by dilution procedures or the sampling technique rather than analytical imprecision.

Discussion

The use of elastomeric pumps for ambulatory delivery of antimicrobials improves autonomy and convenience for patients during anti-infective treatments, not to mention its important impact on healthcare costs. In addition, elastomeric pumps make it possible to choose from a larger number of antimicrobial substances for outpatient treatment, permitting selection of the most appropriate antimicrobial treatment.

Among potential limitations in the use of elastomeric pumps, uncertainty about the stability of antimicrobial drugs in infusion solutions is of concern. In real-life conditions these solutions are indeed maintained over a prolonged period (24 h) and exposed to non-negligible temperature variations.

Our study confirms that during daytime the temperature of antibiotic solutions in pumps progressively increased well above 25°C, the temperature at which most stability studies are conducted. Heat provided by direct exposure to sunlight was found to cause particularly significant increases in temperature. Our experiments also show that antibiotic solutions stored in black carry pouches overheat more than those placed in white carry pouches and that isothermal carry pouches are unable to protect against significant temperature variations. During the night, when the pump remains around the waist in direct contact with the patient's body and is kept under the blanket, the temperature may increase to 32°C.

In order to ensure adequate anti-infective activity, usual recommendations state that antibiotic degradation at the end of the infusion period should be <10% from the initial concentration.[1,2] Our experiments performed in real-life, albeit conservative, conditions, showed that cefazolin, cefepime, piperacillin and tazobactam can be considered stable over 24 h, while flucloxacillin showed a mean decrease in concentration of 11% after 24 h. In spite of this degradation, it is very unlikely that patients could be at risk of insufficient antimicrobial coverage. Our confidence intervals indicate that actual degradation rates are very unlikely to cause more than a 16% decrease in concentration after 24 h.

There are some limitations to these data. The determination of initial antibiotic concentrations at 0 h already showed some variability and deviations in concentrations in the pumps compared with nominal levels. As explained above, this was probably due to imprecision occurring during the preparation of antimicrobial solutions or due to the sampling technique. Furthermore, this study did not examine the production of toxic degradation products and variations in the pH.

In conclusion, our results show that in certain real-life situations the temperature of antimicrobial solutions in elastomeric pumps can greatly exceed the recommended value of 25°C, thus potentially affecting the chemical stability of the drugs. Patients should therefore be instructed to take precautions to prevent excessive temperature increases. Finally, if appropriate precautions are taken, we demonstrated that under real-life conditions no significant degradation of cefazolin, cefepime, piperacillin and tazobactam is observed. For flucloxacillin, degradation of 11% is expected over 24 h, but with questionable impact on the actual efficacy of anti-infective treatment.

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Transparency declarations

None to declare.

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