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

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Running title: Temperature and antibiotic stability in elastomeric pumps

Abstract

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. This study aimed 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.

Healthy volunteers carried the elastomeric pumps in carry pouches during their daily activities. A thermologger measured the temperatures every 15 minutes over 24 hours (h). Antibiotic concentrations were measured by high performance liquid chromatography coupled to tandem mass spectrometry.

During daytime, the temperature of solutions in the pumps increased steadily warming up to above 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 allowed to reduce excessive temperature increases. Over 7 experiments cefazolin, cefepime, piperacillin and tazobactam were found to be stable during 24h. Flucloxacillin showed a mean decrease in concentration of -11% ($p = 0.001$).

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 the 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.

Background

When considering outpatient parenteral antimicrobial therapy (OPAT) for a patient, the selection of the suitable antibiotic should remain guided by the usual criteria of anti-infective therapy (ie. susceptibility of the isolated germs, severity and site of infection) rather than by the availability of some antibiotic that would just be easier to use.[1,2] In that context, elastomeric pumps 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. Especially the stability of the antimicrobials in real-life conditions is poorly known. 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°C, 5°C and 25°C.[4] Actually, only two small studies have explored antibiotics solution stability at a higher temperature of up to 35°C.[5,6]

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

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 during July varied between

4°C and 27°C, and during February between -1° and 12°C. Each experiment was repeated 3 times. Elastomeric pumps of the brand Easypump LT-270-24® (B. Braun Medical Inc, Melsungen, Germany) were used.

The temperature of the solutions in the pumps was measured 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 setup showed to measure temperatures which were very close to the real temperature of the solution in the pumps.

The antimicrobial drugs and concentrations thereof 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/tazobactam 13.5 g. The maximal duration of stability at room temperature (25°C) of these antibiotics diluted in normal saline have 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; tazobactam: 24 h at 10 g/L.[7]

The antimicrobial drugs stability experiments were carried out under the real-life conditions that would cause the smallest temperature variations as identified by above-described experiments. The volunteers were asked to collect 5 mL-aliquot samples from the elastomeric pump at the 0-, 12- and 24-h time points, 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 7 different occasions. Antimicrobial drug concentrations were measured by a validated method of liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) 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 95% confidence interval (CI95%).

Results

Temperature variations over 24 h in real-life situations

Firstly, we evaluated the evolution 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 (SD 0.9°C) and 26.2 (SD 1.0°C), respectively. When the pumps were maintained under the blankets during the night, the temperature of solution increased by 2.6 (SD 1.4°C) over 6 h, while the temperatures decreased by 2.8 (SD 2.9°C) over 6 h when the pumps were kept outside of the blankets.

Secondly, direct exposure of 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 hours of sunlight exposure, reaching a maximum of 38.8°C, while in black pouches the temperature increased by up to +8.3°C per hour, reaching 45.4°C.

Thirdly, the usefulness of isothermal carry pouches was investigated. The volunteers carried simultaneously elastomeric pumps placed in a normal and in an isothermal carry pouch. The type of pouch modified neither the average temperature (26.2; SD 3.3°C versus 25.9; SD 3.0°C respectively, p=0.60), nor the number of measurements above 25°C (60% versus 56.9% respectively, p = 0.45). Only do the curves suggest that the isothermal pouch added some amount of caloric inertia to the system.

Antimicrobial degradation

Figure 2 shows the evolution of the antibiotic concentrations measured at T0, T12 and T24 in elastomeric pumps. Cefazolin, cefepime, piperacillin and tazobactam were found to be stable over 24h with mean degradation after 24 h of +4%, -4%, -2% and -2% respectively. Flucloxacillin however showed a mean decrease in concentration of -11% after 24h. The corresponding slope over time was significantly negative, indicating a degradation half-life of 137 h (CI95%: 93–259 h, p=0.001). On this basis, the relative loss over 24 h was estimated to amount to 11% (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 T0 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 fixed association, 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 the autonomy and the convenience of patients during anti-infective treatments, not to mention its important impact on healthcare costs. In addition elastomeric pumps allow choosing from a larger number of antimicrobial substances for the outpatient treatment, permitting to select 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 duration (24 h) and exposed to non-negligible temperature variations.

Our study confirms that during daytime the temperature of antibiotics 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 increase in temperature. Our experiments also show that antibiotics solutions stored in black carry pouches overheat more than those placed in white carry pouches and that isothermal carry pouches are not efficient to reduce significant temperature variations. During the night, when the pump remains around the waist in direct contact with patient's body and kept under the blanket, the temperature may increase up to 32°C.

In order to ensure adequate anti-infective activity, usual recommendations state that the antibiotic degradation at the end of the infusion period should be less than 10% from the initial concentration.[1,2] Our experiments performed in real-life, albeit under conservative conditions, showed that cefazolin, cefepime, piperacillin and tazobactam can be considered stable over 24 hours, while flucloxacillin showed a mean decrease in concentration of -11% after 24 h. In spite of this degradation, it is very unlikely that it could put patients at risk of insufficient antimicrobial coverage. Our confidence intervals indicate that actual degradation rates have very little chances to reach -20%.

There are some limitations to these data. The determination of initial concentrations at T0 already showed some variability and deviations in the antibiotic concentrations in the pumps compared to 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 didn't look at 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 largely exceed the recommended temperature 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. If appropriate precautions are taken, we finally demonstrate 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, however with questionable impact on the actual efficacy of anti-infective treatment.

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Transparency declarations

The authors have no conflict of interest to declare.

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193 **Figure 1.** Evolution of temperature in two elastomeric pumps worn by the same volunteer, one carried
194 attached around the waist (continuous line) and one detached (dashed line) during night time
195 (shadowed area).

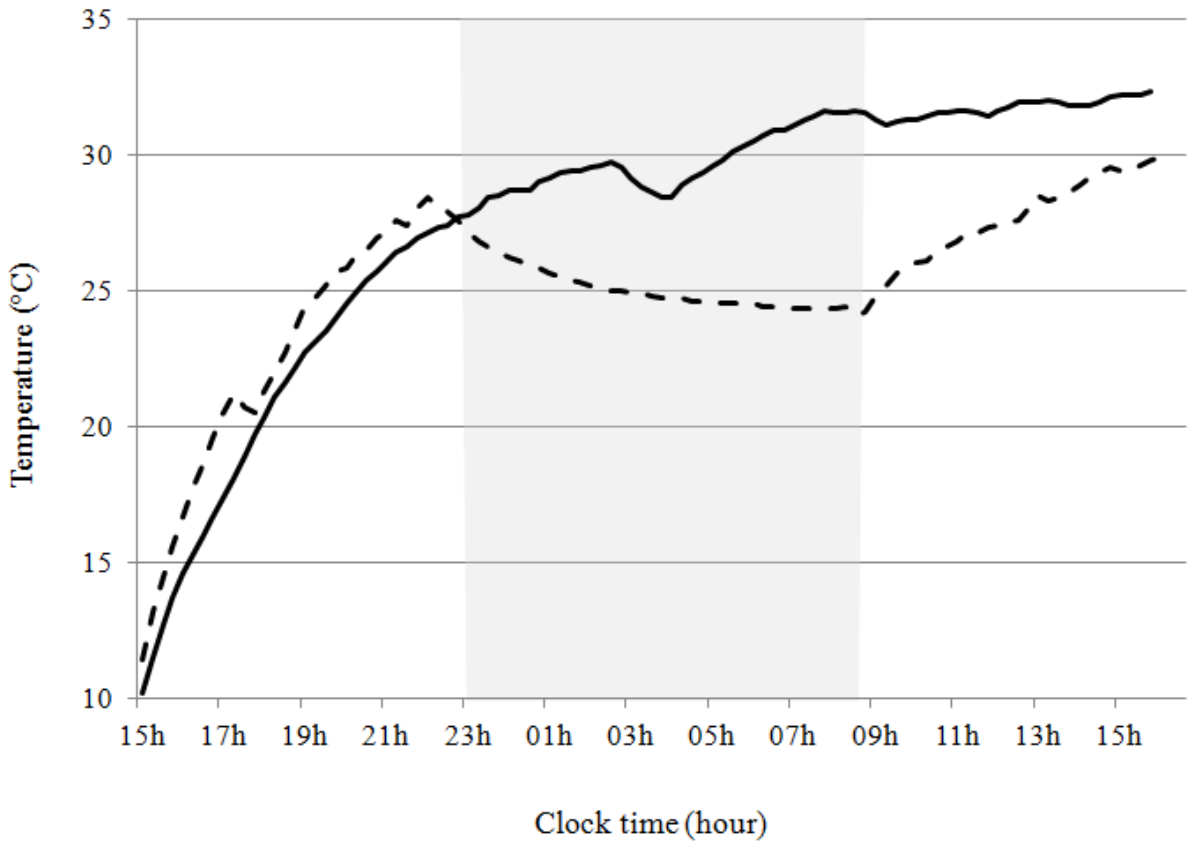

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Figure 2. Degradation of antibiotics in elastomeric pumps sampled at 0, 12 and 24 h under real-life conditions indicated as mean concentration and standard deviation