Title: Adequate plasma drug concentrations suggest that amoxicillin can be administered by continuous infusion using elastomeric pumps.

Authors: Arensdorff L, Boillat-Blanco N, Decosterd L, Buclin T, de Vallière S

Journal: The Journal of antimicrobial chemotherapy

Year: 2017 Sep 1

Issue: 72

Volume: 9

Pages: 2613-2615

DOI: 10.1093/jac/dkx178

Adequate plasma drug levels suggest that amoxicillin can be administered by continuous infusions using elastomeric pumps

Lyne Arensdorff[1], Noémie Boillat-Blanco[1,2], Laurent Decosterd[3], Thierry Buclin[4], Serge de Vallière[1,2]

[1] Department of Ambulatory Care and Community Medicine, University Hospital of Lausanne, Switzerland

[2] Service of Infectious Diseases, University Hospital of Lausanne, Switzerland

[3] Laboratory of Clinical Pharmacology, Service of Biomedicine, University Hospital of Lausanne, Switzerland

[4] Division of Clinical Pharmacology, Service of Biomedicine, University Hospital of Lausanne, Switzerland

Serge de Vallière

Infectious Diseases Service, and

Department of Outpatient Care and Community Medicine

University Hospital of Lausanne

Av du Bugnon 44, 1011 Lausanne, Switzerland

Phone : +41 79 556 43 12 ; Fax : +41 314 48 57

Email : serge.de-valliere@hospvd.ch

Abstract:

Background: In the outpatient setting elastomeric pumps are useful for the continuous administration of antibiotics with time-dependent bacterial killing activity such as amoxicillin.

Objective: To determine the amoxicillin degradation in elastomeric pumps, as well as the effectiveness of treatment by verifying plasma drug levels and clinical outcome of patients treated in this way.

Methods: Elastomeric pumps were filled with 6 g and 4 g /240 ml of NaCl 0.9%. Degradation was measured in the pumps filled with 6 g of amoxicillin by drawing samples at 12 hour intervals when stored in the fridge for 48 hours and when worn around the waist for 24 hours. Subsequently 9 patients were treated with continuous infusions of 8 g or 12 g of amoxicillin per day. Plasma amoxicillin levels were measured on each visit to the OPAT unit. Clinical outcome was verified 3 months after the end of treatment.

Results: Amoxicillin degradation in elastomeric pumps filled with 6 g of amoxicillin /240 ml of NaCl 0.9% reached 10% after 48 hours in the fridge and an additional 30% when worn around the waist for 24 hours. Despite this significant degradation, mean plasma drug levels achieved with 12 g of amoxicillin per day were 18.5 mg/L (95%CI 13.5-23.5), which is largely above the MIC of amoxicillin-sensitive bacteria. 9 patients treated for various infections for a median of 28 days were cured and had no unexpected adverse effects.

Conclusion: Adequate plasma drug levels and favourable clinical outcome suggest that amoxicillin can be administered by continuous infusions using elastomeric pumps. This treatment modality does not fulfil formal requirements regarding pharmaceutical stability. Still the resulting safety impact in patients is probably limited. Therapeutic drug monitoring and a close clinical follow up are recommended if this route of administration is chosen.

Introduction:

In the setting of outpatient parenteral antibiotic therapy (OPAT), elastomeric pumps can be useful devices for the continuous administration of antibiotics with time-dependent bacterial killing activity. The continuous infusion with elastomeric pumps notably avoids the need for multiple daily interventions of healthcare workers at patient's home or multiple visits of the patient to the OPAT unit.

A limiting factor for the use of elastomeric pumps is the potential drug instability in these devices over the infusion period. Generally, an antibiotic degradation remaining below 10% of the initial concentration is considered acceptable even though this limit has been chosen mostly arbitrarily.[1] Stability data of antibiotic solutions in elastomeric pumps has been mostly published by manufacturers of these devices and they usually report the maximal duration of the drug stability at 5°C (fridge) and 25°C tested under standardised laboratory conditions. However, in the real-world setting the antibiotic solutions are exposed to temperatures that can rise well above 25°C.[2]

For amoxicillin, the published stability data is contradictory. A study published by Arlicott et al suggests a reasonable stability in elastomeric pumps from the manufacturer Baxter.[3] Indeed this study indicates a drug degradation of less than 10% at concentrations of 20 and 40 g/L when exposed to temperatures of 20°C and 35°C for 24 hours. Toxikon Europe NV, Leuven, Belgium, which tested the stability of amoxicillin in the elastomeric pumps from the manufacturer B. Braun Medical, indicates however a stability at 25°C of only 4 and 2 hours at concentrations of 1g/L and 40 g/L, respectively, without giving any detailed data about their

experiments.[4] According to this source the stability of amoxicillin, when kept refrigerated, is 6 hours. Although these experiments were conducted by using elastomeric pumps of different brands, there is no reason to expect such important differences between devices.

In this study, we investigated if amoxicillin could be administered by elastomeric pumps by 1) evaluating the antibiotic degradation in these devices, 2) measuring the plasma drug levels and 3) verifying the clinical outcome of 9 patients treated.

Methods

Elastomeric pumps (Easypump LT-270-24®, B. Braun Medical Inc, Melsungen, Germany) were filled with amoxicillin 6 g or 4g/240 ml NaCl 0.9% without buffering agent by the pharmacy under sterile conditions using a laminar flow cabinet. The devices were stored for up to 48 hours in the fridge at 5°C.

Before treating any patients, we measured, on three different occasions, the antibiotic degradation in elastomeric pumps filled with 6 g of amoxicillin/240 ml NaCl 0.9%, stored in the fridge for 48 hours and then carried by volunteers around the waist for 24 hours.

Based on these results our pharmacokinetic calculations indicated that continuous infusions with elastomeric pumps would still achieve amoxicillin plasma levels above 4 mg/L despite the measured antibiotic degradation. The minimal inhibitory concentration for amoxicillin sensitive gram-positive cocci being 4 mg/L or less[5], we considered that we would not put

patients at risk of treatment failure. We therefore subsequently treated 9 patients with continuous amoxicillin administration by elastomeric pumps.

Patients were provided with prepared elastomeric pumps, which they stored in their fridge at home. The pumps were either changed by the patients themselves, by home-based nurses or at the OPAT-unit. Amoxicillin plasma levels were drawn when patients visited the OPAT clinic for clinical follow-up, in principle every 7 days.

The patients' clinical outcome of was evaluated 3 months after the end of the treatment. Patients were considered cured if they had not been re-started on antibiotic treatment or re-admitted to hospital for the same problem. This was verified by checking the electronic hospital records. Considering that these patients were all treated for serious infections, we considered that all patients with failing treatment would most probably be re-admitted.

Results:

After 48 hours storage in the fridge at 5°C the mean concentration decreased from 29.0 ± 0.9 g/L to 26.4 ± 1.4 g/L (-9%). When the elastomeric pumps were carried by volunteers for 24 hours, the antibiotic concentration decreased from a mean 26.4 ± 1.4 g/L to 18.0 ± 2.2 g/L (-32%).

Table 1 shows the demographic details, the pathologies, the micro-organisms responsible and the plasma drug levels for the 9 patients treated. All patients had normal renal functions with

creatinine clearances > 60 ml/min and they were treated as outpatients for a median of 28 days (range 7- 36 days).

The results of the plasma drug levels are summarised in Figure 1. The continuous infusions of 8 g and 12 g of amoxicillin provided mean plasma levels of 5.1 mg/L (95%CI 0.1 – 10.1) and 18.5 mg/L (95%CI 13.5-23.5), respectively.

None of the patient had any significant side-effects and all patients were considered cured 3 months after the end of treatment.

Discussion:

Despite a significant drug degradation exceeding the legally tolerated limit of 10%, this data suggests that a continuous infusion of amoxicillin using elastomeric pumps can ensure efficacious concentration exposure. Our observations indicate that the mean plasma drug levels of 18.5 mg/L are overall sufficient in patients treated with 12 g per day of amoxicillin administered by a continuous infusion using elastomeric pumps. Caution should be exercised with patients on 8 g amoxicillin per day, as the mean plasma levels of 5.1 mg/L were only slightly above the target levels recommended for enterococci. In comparison amoxicillin has an average serum half-life of 1.2 hours and a rapid infusion of amoxicillin 2 grams results in plasma levels of 50.2 mg/L after 1 hour, 16.3 mg/L after 2 hours and 3.3 mg/L after 4 hours.

There are several possible explanations for the low plasma levels of 0.9 mg/L and 2.4 mg/L found in 2 patients receiving the 12 gram dose. First there could have been a problem with the

storage or the continuous flow of the antibiotic solution, but the patients didn't report any such problem. Secondly, improper collection and delayed transport of the blood specimens before analysis could be a reason. Of note, plasma levels determined in these two same patients on 3 and 2 additional occasions showed mean concentrations of 12.2 mg/L and 27.0 mg/L, respectively.

Besides the plasma drug levels, the clinical data is also reassuring as all patients were cured 3 months after the end of treatment, and no patient had any unexpected adverse effects.

These results should be put in perspective with the current recommendations that antibiotic degradation should not exceed 10% of the nominal concentrations of the solution introduced into elastomeric devices. The legislation is certainly clear about this point, but on the other hand it is known that amoxicillin is mainly converted to penicilloic acid, also formed through in vivo degradation of amoxicillin and essentially devoid of toxicity (but probably involved in immuno-allergic reactions).

In conclusion continuous infusion with elastomeric pumps, at suitable antibiotic doses, provided sustained amoxicillin levels well over the MIC of amoxicillin-sensitive bacterial micro-organisms, and was clinically efficacious. Future studies aiming at determining whether a given antibiotic can be administered using elastomeric pumps should certainly consider the drug's physico-chemical stability in the elastomeric devices – assessed in real-life conditions. Still, it is also important to take into account the potential pharmacokinetic impact in patients, in addition to thorough clinical follow up for safety and tolerability. To

that endeavour, therapeutic drug monitoring is recommended for ascertaining antibiotic plasma exposure in patients receiving prolonged infusion *via* elastomeric pumps.

Funding

The project was supported by an unconditional grant from the Swiss General Internal Medicine Foundation.

Transparency declarations

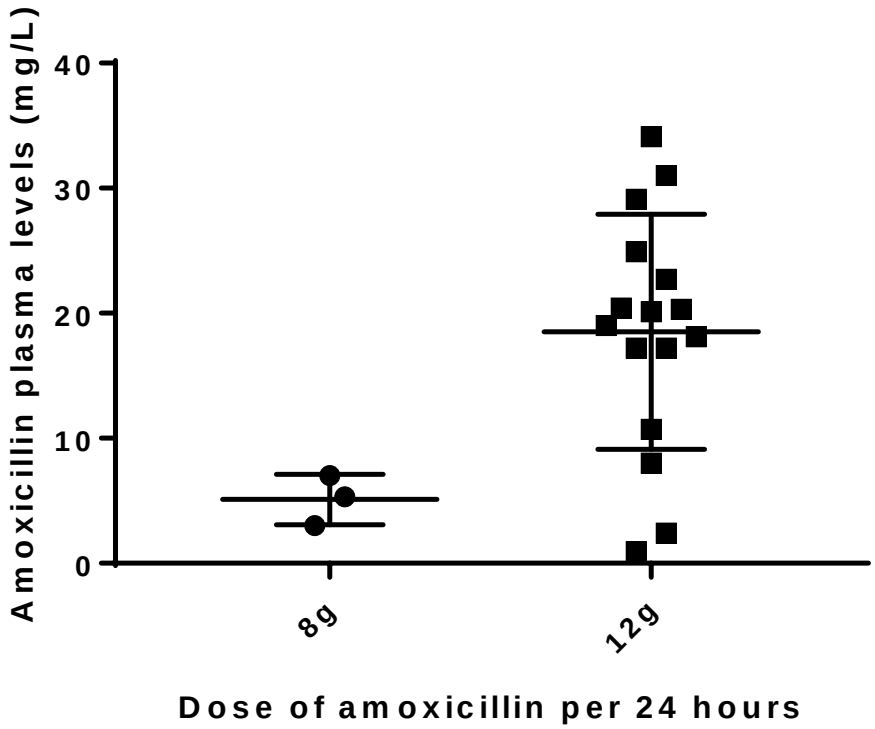
The authors have no conflict of interest to declare.

170 Table.

Sex / age (y)	Diagnosis	Infecting bacteria	MIC (mg/L)	Duration of treatment (days)	Type of support for administration	Dose (grams)	Drug level 1 (mg/L)	Drug level 2 (mg/L)	Drug level 3 (mg/L)	Drug level 4 (mg/L)
M/83	Prosthetic valve endocarditis	*E. faecalis*	0.75	28	Home-based nurses	12	31			
F/57	Prosthetic valve endocarditis	*E. faecalis*	NA	29	Self-administration	12	20.3	17.2	19	
M/35	Osteomyelitis + infection of hardware	*E. faecalis*	NA	31	Self-administration	12	18.1	10.7	8	0.9
M/78	Prosthetic valve endocarditis	*E. faecalis*	NA	21	Home-based nurses	12	2,4	24,9	29,1	
M/85	Native valve endocarditis	*E. faecalis*	1.0	14	Home-based nurses	12	34,1	20,1		
M/46	Native valve endocarditis	*Strep. mitis*	NA	28	Self-administration	12	22,7	19,2	22,9	17,2
M/75	Native valve endocarditis	*E. faecalis*	NA	21	Home-based nurses	12	20,4	17,2		
M/71	Febrile agranulocytosis	*E. faecalis*	NA	7	OPAT-unit	8	3			
F/66	Osteomyelitis + infection of hardware	*E. faecalis*	NA	36	Self-administration	8	7	5.3		

171

Figure 1. Amoxicillin plasma levels (mean ± SD) according to total daily dose of amoxicillin administered as continuous infusions with elastomeric pumps.



176 **References:**

[1] Dellamorte Bing C, Nowobilsk-Vasilios A. Extended Stability for parenteral drugs, American Society of Health-System Pharmacists. 2013, 5th edition.

[2] Voumard R, Van Neyghem N, Cochet C, Gardiol C, Decosterd L, Buclin Th, de Vallière S. Antibiotic stability related to temperature variation in elastomeric pumps used for outpatient parenteral antimicrobial therapy (OPAT). Journal of Antimicrobial Chemotherapy 2017, doi: 10.1093/jac/dkw582. [Epub ahead of print]

[3] Arlicot N, Marie A, Cade C, Laffon M, Antier D. Stability of amoxicillin in portable pumps is drug concentration dependent. Pharmazie 2011; 65:631-2.

[4] B.Braun Medical. Drug stability for Easypump II. Available at www.bbraun.nl/documents/Products/Drug_Stability_09_10_12.pdf. Accessed on 28.2.2017.

[5] Eucast : Antimicrobial wild type distributions of microorganisms. http://mic.eucast.org/Eucast2/SearchController/search.jsp?action=performSearch&BeginIndex=0&Micdif=mic&NumberIndex=50&Antib=175&Specium=-1. Accessed on 28.2.2017.