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

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Background: Elastomeric pumps can be useful for the administration of antibiotics in the outpatient setting.

Objectives: To determine amoxicillin degradation in elastomeric pumps, as well as the effectiveness of amoxicillin treatment administered by elastomeric pumps.

Methods: Antibiotic degradation was measured in elastomeric pumps filled with 6 g of amoxicillin in 240 mL of NaCl 0.9% by drawing samples at 12 h intervals when stored in the fridge for 48 h and when worn around the waist for 24 h. Subsequently nine patients were treated with continuous infusions of 8 or 12 g of amoxicillin per day. Plasma amoxicillin concentrations were measured on each visit to the outpatient parenteral antibiotic therapy unit. Clinical outcome was verified 3 months after the end of treatment.

Results: Amoxicillin degradation in elastomeric pumps reached 10% after 48 h in the fridge and an additional 30% when worn around the waist for 24 h. Mean plasma drug concentrations 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-susceptible bacteria. Nine patients treated for various complicated infections were cured and had no unexpected adverse effects.

Conclusions: Adequate plasma drug concentrations and favourable clinical outcomes suggest that amoxicillin can be administered by continuous infusion using elastomeric pumps. This treatment modality does not fulfil formal requirements regarding pharmaceutical stability, but 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. Notably, continuous infusion with elastomeric pumps avoids the need for multiple daily interventions by healthcare workers at the 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 <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 have been mainly 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 standardized laboratory conditions. However, in real-world settings the antibiotic solutions are exposed to temperatures that can rise well above 25°C.[2]

For amoxicillin, the published stability data are contradictory. A study by Arlicot *et al.*[3] suggests reasonable stability in elastomeric pumps from the manufacturer (Baxter). That study indicates a drug degradation of <10% at concentrations of 20 and 40 g/L when exposed to temperatures of 20°C and 35°C for 24 h. Toxikon Europe NV (Leuven, Belgium) tested the stability of amoxicillin in elastomeric pumps from the manufacturer B. Braun Medical, and indicated only a stability at 25°C of 4 and 2 h at concentrations of 1 and 40 g/L, respectively, without giving detailed data about their experiments.[4] According to that source, the stability of amoxicillin when kept refrigerated is 6 h. Although these experiments were conducted with elastomeric pumps of different brands, there is no

Table 1. Details of the nine patients treated with amoxicillin by continuous infusion using elastomeric pumps

Sex/ age (years)	Diagnosis	Infecting bacteria	MIC (mg/L)	Duration of treatment (days)	Type of support for administration	Dose (g/day)	Plasma drug concentration (mg/L) sample 1	sample 2	sample 3	sample 4
M/83	prosthetic valve endocarditis	*Enterococcus 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	*Streptococcus 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		

NA, not available.

reason to expect such significant differences between different devices.

In this study, we investigated whether amoxicillin was suitable for administration by elastomeric pumps by: (i) evaluating the antibiotic degradation in these devices; (ii) measuring the plasma drug concentrations; and (iii) verifying the clinical outcomes in nine patients.

Patients and methods

Elastomeric pumps (Easypump LT-270-24®; B. Braun Medical Inc., Melsungen, Germany) were filled with amoxicillin 6 or 4 g in 240 mL of NaCl 0.9% without buffering agent by the pharmacy under sterile conditions in a laminar flow cabinet. The devices were stored for up to 48 h 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 in 240 mL of NaCl 0.9%, stored in the fridge for 48 h and then carried by volunteers around the waist for 24 h.

Based on these results our pharmacokinetic calculations indicated that continuous infusions with elastomeric pumps would still achieve amoxicillin plasma concentrations >4 mg/L despite the measured antibiotic degradation. As the MIC for amoxicillin-susceptible Gram-positive cocci is ≤4 mg/L,[5] we considered that we would not put patients at risk of treatment failures. Therefore, we subsequently treated nine patients with continuous amoxicillin administration by elastomeric pump.

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. Blood samples were drawn for determination of amoxicillin concentrations in plasma when patients visited the OPAT clinic for clinical follow-up, in principle every 7 days.

The clinical outcome of the patients was evaluated 3 months after the end of treatment. Patients were considered as cured if they had not been restarted on antibiotic treatment or readmitted to hospital for the same problem. This was verified by checking the electronic hospital records.

Results

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

Table 1 shows the demographic details, pathologies, responsible microorganisms and plasma drug concentrations for the nine 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 plasma drug concentration data are summarized in Figure 1. The continuous infusions of 8 and 12 g of amoxicillin provided mean plasma concentrations 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 patients had any significant side effects and all were considered as cured 3 months after the end of treatment.

Discussion

Despite significant drug degradation, exceeding the limit of 10% tolerated by regulations, these data suggest that a continuous infusion of amoxicillin using elastomeric pumps can ensure efficacious concentration exposure. Our observations indicate that the mean plasma drug concentrations of 18.5 mg/L are overall sufficient in patients treated with 12 g/day of amoxicillin administered by continuous infusion using an elastomeric pump. Caution should be exercised with patients on 8 g/day of amoxicillin, as the mean plasma concentrations of 5.1 mg/L were only slightly above the target levels recommended for enterococci. In comparison, a rapid infusion of amoxicillin 2 g results in plasma concentrations of 50.2 mg/L after 1 h, 16.3 mg/L after 2 h and 3.3 mg/L after 4 h. As amoxicillin is an antibiotic with time-dependent killing activity,

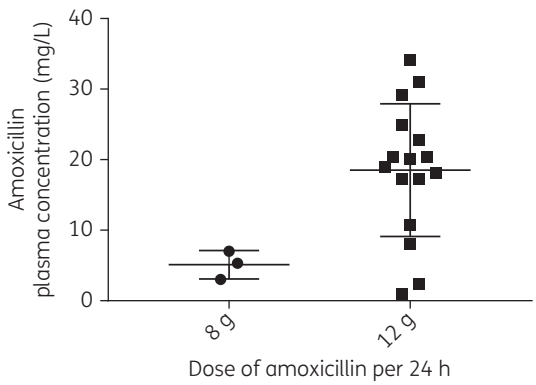

Figure 1. Amoxicillin plasma concentrations (mean ± SD) according to total daily dose of amoxicillin administered as continuous infusions with elastomeric pumps.

continuous infusions with elastomeric pumps should therefore be at least as efficacious as intermittent administration.

There are several possible explanations for the low plasma concentrations of 0.9 and 2.4 mg/L found in two patients receiving the 12 g/day dose. First, there could have been a problem with the storage or the continuous flow of the antibiotic solution, but the patients did not report any such problem. Second, improper collection and delayed transport of the blood specimens before analysis could be a reason. Notably, the plasma concentrations determined in the same two patients on three and two additional occasions showed mean concentrations of 12.2 and 27.0 mg/L, respectively.

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

These results should be put into perspective with the current recommendations that antibiotic degradation should not exceed 10% of the nominal concentrations of the solution introduced into the elastomeric device. Regulations are certainly clear about this point, but on the other hand, it is known that amoxicillin is mainly converted to penicilloic acid, which is also formed through *in vivo* degradation of amoxicillin and is essentially devoid of toxicity, except probably for immunoallergic reactions.

In conclusion, using suitable antibiotic doses, continuous infusion with elastomeric pumps provided sustained amoxicillin levels well over the MIC of amoxicillin-susceptible bacteria, and was clinically efficacious. Future studies aiming to determine 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 end, therapeutic drug monitoring can be recommended for ascertaining antibiotic plasma exposure in patients receiving prolonged infusion via elastomeric pumps.

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Transparency declarations

None to declare.

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