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Taurolidine is effective in the treatment of central venous catheter-related bloodstream infections in cancer patients

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Abstract

Taurolidine is an antimicrobial agent that was originally used in the local treatment of peritonitis and was shown to be effective in the prevention of catheter-related bloodstream infections (CR-BSI). In this pilot study, we used taurolidine solution as an intravenous (i.v.) lock into the totally implantable intravascular devices of 11 consecutive oncological patients with catheter-related bloodstream infections not responding to systemic antimicrobial chemotherapy. All patients recovered completely from the infection. No adverse drug effects were seen. Three patients were successfully retreated for a recurrent infection. Our data suggest a beneficial role of taurolidine i.v. lock for the therapy of catheter-related bloodstream infections in oncological patients. Taurolidine i.v. lock application is feasible and could especially be useful in infections resistant to antibiotic chemotherapy.

Keywords: Totally implantable intravascular devices; Taurolidine; Antimicrobial lock solution; Bloodstream infections; Treatment

1. Introduction

Venous access is a critical issue in the care and management of many malignancies since these patients frequently require not only i.v. cytostatic chemotherapy but parenteral nutrition and hydration, analgesic therapy, treatment of infections and repetitive laboratory work up. Thus, the placement of indwelling central catheters such as Broviac and Hickman catheters or of port catheter systems enabling safe and permanent venous access is strongly recommended due to physical and psychological factors associated with repeated venepuncture secondary to the loss of peripheral venous access [1,2]. The use of permanent central venous access systems has increased steadily in the last two decades but was accompanied by a simultaneous increase of complications, mainly by a variety of local and systemic catheter-related infections [3–5]. Catheter-related bacteraemia or septicaemia may be secondary to a local infection at the site of skin puncture, haematogenous seeding of bacteria from a distant focus or may be associated with contamination of the solution or administration set (fluids or parenteral nutrition mixtures). In about two-third of cases, the organisms causing catheter-related bloodstream infections (CR-BSI) are skin commensals such as coagulase negative staphylococci emphasising the relevance of proper skin care and hand washing for adequate prevention [6].

New approaches to make intravascular catheters more resistant to bacterial colonization are under investigation. These include antiseptic or antibiotic coating of the catheter surface, impregnation of cuffs with silver ions and antiseptic hubs [7]. The antiseptic agent taurolidine is a derivative of taurinamide, a naturally occurring aminosulphonic acid, and formaldehyde. Taurolidine has an exceptionally broad spectrum of antimicrobial activity including activity against Gram negative and Gram positive bacteria and fungi. Emergence of bacterial resistance to taurolidine has not been demonstrated. The antimicrobial properties of taurolidine have been ascribed

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to the biologically active methylol taurinamide which reacts with cell wall constituents of microbial pathogens via methylene iminium ions preventing bacterial adhesion to biological surfaces [8,9]. Additional proposed mechanisms of action of taurolidine include the capability to reduce tumour necrosis factor (TNF)-α synthesis and activity [10,11] and interaction with cell surface structure and function [12]. Taurolidine has been shown to be non-toxic to human and animals. It has a short half-live and is metabolised to taurine, carbon dioxide and water. The extent of its antimicrobial activity in vitro and in vivo is well documented in several studies [8,13–17]. Recent clinical publications report that taurolidine is effective in the prevention of urinary tract infections subsequent to urinary catheterisation and haemodialysis catheter-related infections and that its intravenous and intraperitoneal administration is not associated with noteworthy side effects [18–22]. The efficacy of taurolidine in infected indwelling central venous catheters or port catheter systems has only been described in a few case reports and has not yet been analysed in a greater panel of patients within the scope of a randomised or non-randomised clinical study [23].

2. Patients and methods

Our trail was designed as an open non-randomised single centre pilot study and was conducted at the Department of Haematology, Oncology and Immunology, St. Johannes Hospital Duisburg, Germany. Hospitalised adult patients with proven CR-BSI related to totally implantable intravascular devices (TID) who did not respond to 48–72 h of i.v. antibiotic chemotherapy were eligible. Eleven consecutive patients (three male and eight female individuals) with a mean age of 64.5 years were enrolled in this study. Diagnoses included solid tumours (n = 8), chronic lymphatic leukaemia (CLL) (n = 1) and lymphoma (n = 2). Criteria for exclusion from the study were a history of allergy to taurolidine, risk factors for catheter-related central venous thrombosis, purulence of the catheter exit site or local catheter pocket infection and catheter infections with fungal pathogens. The decision to remove catheters was made by the medical staff without influence of the investigators. All patients enrolled or their legal guardians gave informed consent for the treatment with taurolidine in CR-BSI. The trial was approved by the local internal review board.

3. Assessment of CR-BSI

CR-BSI was diagnosed on the basis of typical clinical signs of bloodstream infection (temperature >38 °C, chills, arterial hypotension and a raised or lowered peripheral white blood count (WBC)) with the catheter as the only obvious source of infection. In addition, isolation of the same organism (identical species and antibiogram) from catheter culture and peripheral blood culture was regarded as direct evidence. In patients with clinically suspected CR-BSI repetitive, peripheral blood samples and catheter swabs were collected for culture. Isolated organisms were identified by standard microbiological methods. Before administration of taurolidine, a complete physical examination was performed as well as laboratory workup including differential WBC, electrolytes, liver function tests, creatinine and C-reactive protein (CRP). After taurolidine administration, the course of CR-BSI was monitored by clinical assessment and close-meshed investigation of central and peripheral venous blood cultures.

4. Treatment of CR-BSI

Patients with proven CR-BSI who did not respond to i.v. antibiotic treatment received a taurolidine i.v. lock in addition to systemic antibiotic chemotherapy according to the antibiogram. We administered 3 ml taurolidine-ringer 0.5% into the devices and left them closed for 24 h. Hereafter, the device was flushed with 10 ml NaCl 0.9%. In order to evaluate the effect of repeated taurolidine administration, in two patients the treatment was repeated after 24 h and in three patients after 24 and 48 h.

5. Results

5.1. Microbial isolates and treatment

Microbial isolates from peripheral blood and devices of patients with CR-BSI included coagulase negative *Staphylococcus* spp. (n = 4), *Acinetobacter baumannii* (n = 2), *Stenotrophomonas maltophilia* (n = 1), *Staphylococcus aureus* (n = 1), *Escherichia coli* (n = 1), *Pseudomonas picketti* (n = 1) and *Pseudomonas aeruginosa* (n = 1). Systemic antibiotic regimes following the antibiogram were initiated and taurolidine i.v. lock solutions were administered as described above.

5.2. Treatment response

Six patients received a single course of 1 × 3 ml taurolidine, two patients received 1 × 3 ml taurolidine on two consecutive days and three patients received 1 × 3 ml taurolidine on three consecutive days as a lock solution into the devices (Table 1). All patients recovered completely from CR-BSI (disappearance of clinical symptoms, normalization of CRP values, negative blood cultures) without replacement of the devices (Table 2).

A recurrent episode of CR-BSI was observed in three patients during the study period and was again successfully treated with taurolidine i.v. lock (Table 3). The first case was a patient with *A. baumannii* and oxacillin resistant *Staphylococcus* spp. isolates in the device during the first episode that had been treated with one injection of taurolidine. Two months later *A. baumannii* and coagulase negative

Table 1
Microbial isolates and treatments

Patient number	Microbial isolates		Antimicrobial treatment	
	Catheter	Peripheral blood	Antibiotics	Taurolidine 0.5%
1	Not done	*Pseudomonas aeruginosa*	Ceftazidime	1 × 3 ml
2	*A. baumannii*, oxacillin rest. *Staphylococcus* spp.	No growth	Imipenem	1 × 3 ml
5	*A. baumannii*	*A. baumannii*	Ceftazidime, gentamicin	1 × 3 ml
7	*Staphylococcus aureus*	Not done	Cefazolin, sultamicillin	1 × 3 ml
8	Coagulase negative *Staphylococcus* spp.	Coagulase negative *Staphylococcus* spp.	Ciprofloxacin, ceftriaxone	1 × 3 ml
10	*E. coli*	*E. coli*	Tazobactam, piperacillin, gentamicin, metronidazole	1 × 3 ml
3	Coagulase negative *Staphylococcus* spp.	Coagulase negative *Staphylococcus* spp.	Ceftazidime, gentamicin	2 × 3 ml
11	Coagulase negative *Staphylococcus* spp.	Coagulase negative *Staphylococcus* spp.	Imipenem, vancomycin	2 × 3 ml
4	*A. baumannii*	*A. baumannii*	Sultamicillin,	3 × 3 ml
6	*A. baumannii, Pseudomonas picketti*	*A. baumannii*	Tazobactam, piperacillin	3 × 3 ml
9	Coagulase negative *Staphylococcus* spp.	Coagulase negative *Staphylococcus* spp.	Tazobactam, piperacillin, gentamicin	3 × 3 ml

Table 2
Patient characteristics before and after taurolidine treatment

Number of patients	Sex (m/f)	Mean age (years) (range)	Diagnosis	Before taurolidine			After taurolidine		
				Mean WHO performance status (range)	Mean WHO fever grade (range)	Mean WHO infection grade (range)	Mean WHO performance status (range)	Mean WHO fever grade (range)	Mean WHO infection grade (range)
11	3/8	64.5 (41–76)	Solid tumour (n = 8) Leukaemia (n = 1) Lymphoma (n = 2)	2.4 (1–3)	1.9 (1–2)	2.8 (1–3)	1.5 (0–3)	0	0

Staphylococcus spp. were detected within the device. The second patient had been treated with taurolidine i.v. locks on three consecutive days for an *A. baumannii* positive CR-BSI. Three months after initial treatment she had a new CR-BSI with *Stenotrophomonas maltophilia* within the device. In the third case, the device was reinfected with the same isolate (coagulase negative *Staphylococcus* spp.) four months after the initial treatment with taurolidine injections into the device on three consecutive days. After re-treatment with taurolidine i.v. lock application all three patients recovered completely from the CR-BSI.

5.3. Side effects of taurolidine

None of our patients showed local or systemic hypersensitivity reactions, haematological side effects or other organ toxicities associated with the use of taurolidine. In particular, no differences were observed between patients who

Table 3
Microbial isolates and re-treatment

Patient number	Microbial isolates		Antimicrobial treatment	
	Catheter	Peripheral blood	Antibiotics	Taurolidine 0.5%
2	*A. baumannii*, coagulase negative *Staphylococcus* spp.	*A. baumannii*	Cefuroxime, gentamicin	1 × 3 ml
4	*Stenotrophomonas maltophilia*	*Stenotrophomonas maltophilia, Alcaligenes* spp.	Tazobactam, piperacillin	1 × 3 ml
10	Coagulase negative *Staphylococcus* spp.	Coagulase negative *Staphylococcus* spp.	Tazobactam, piperacillin, gentamicin	3 × 3 ml

received only one or those who received more than one application.

6. Discussion

TID are frequently used in patients with oncological diseases. CR-BSI is a major complication of TID which often leads to hospital readmission. For the prevention of these infections, sterile handling of the catheter is crucial. Recent comparative studies have shown that the use of central venous catheters impregnated either with minocycline and rifampicin or with chlorhexidine and silver sulfadiazine is associated with lower rates of catheter colonization and bloodstream infection than the use of unimpregnated catheters [24,25]. Being confronted with nosocomial organisms, often resistant to multiple therapeutic agents, it is important to avoid the prophylactic use of agents used in the treatment of CR-BSI, such as glycopeptides, β-lactams, aminoglycocides, quinolones and azoles [26]. Longuet et al. [27] reported a limited efficacy of treatment with antibiotic lock technique in patients with CR-BSI. The standard therapy consists of systemic antibiotic chemotherapy and often the central venous catheter will be removed. However, in many of these cases the removal of the TID is not necessarily the only therapeutic choice especially taking into consideration that the morbidity associated with insertion of a new central line is significant. The clinical experiences with recurrent CR-BSI suggest that conventional therapy with systemic antibiotics such as vancomycin complemented with antibiotic lock technique and possibly catheter replacement is not successful in stopping recurrence and avoidance of fungal infections. Thus, there is a strong clinical need for alternative treatment approaches in order to improve the management of this dangerous complication in critically ill patients. Taurolidine has been used clinically extensively due to its antimicrobial and antiendotoxaemic properties, particularly in peritonitis [28,29]. Experiences with taurolidine in combination with citric acid and other agents have been reported by Sodemann et al. in patients with end stage renal disease undergoing haemodialysis via subcutaneous port systems [20,30]. The addition of taurolidine to total parenteral nutrition solutions at a concentration above the minimum inhibitory concentration of the commonly encountered staphylococci could be a way of introducing bactericidal conditions against contaminating organisms so protecting against many of the frequent septic complications associated with total parenteral nutrition [31,32]. In our study, taurolidine proved to be a promising agent for the treatment of CR-BSI being successful in all 11 cases including a patient with a line that had previously been endoluminally infected. In addition, an antimicrobial response was also observed in three patients who had prior exposure to taurolidine and a recurrent CR-BSI several months later. No adverse effects were documented.

Our observations suggest a beneficial role of taurolidine i.v. lock application for the therapy of CR-BSI in oncology patients. It acts synergistically with systemic antibiotic chemotherapy resulting in a high rate of complete recovery without replacement of the device. A single injection of taurolidine into the device is sufficient to be effective but repeated administration in patients with recurrent CR-BSI is possible with apparently no loss of efficacy. Taurolidine is characterised by an extraordinary broad antimicrobial activity associated with excellent tolerability in the absence of side effects and drug interactions. Its non-toxic and therapeutic effectiveness justifies its use in patients with CR-BSI and it could be especially useful in infections resistant to antibiotic chemotherapy. Further randomised studies with larger patient numbers will be required to verify the efficacy of taurolidine in this setting.

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