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Clinical experience with Timentin in severe hospital infections

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Sixty-four severe infections in hospitalized patients were treated with intravenous Timentin. Most patients (mean age: 50·5 years, range 18–85) had serious underlying conditions such as agranulocytosis, heart failure, cancer, diabetes mellitus, chronic alcoholism or other functional or anatomical abnormalities. Forty-three episodes were bacteriologically proved, and bacteraemia was diagnosed in 18. The sites of infection were: lower respiratory tract (10), upper respiratory tract (10), soft tissues (9), urinary tract (7), bones (6), peritoneal cavity (3), meninges (1) and pelvis (1). In addition, 13 episodes of fever and four of septicaemia in patients with agranulocytosis were treated with Timentin plus amikacin. Overall, 59% of the episodes were cured, 14% improved and 17% failed to respond. In 9% of cases the efficacy of the Timentin was unassessable mainly because of concurrent administration of other antimicrobials. Failure appeared to be more frequent in soft tissue and intra-abdominal infections, in patients infected with bacteria susceptible to Timentin but resistant to ticarcillin and in patients superinfected with Timentin-resistant strains. Major side effects were haemorrhagic diathesis with platelet dysfunction (1), severe water sodium overload (1), and possibly pancreatitis (1). Other side effects were mild: catheter-related phlebitis, and abnormal but clinically insignificant laboratory test results. Timentin appears to be an effective and safe broad-spectrum combination which compares favourably with third-generation cephalosporins in the treatment of severe hospital infections. More experience is needed to decide whether the somewhat lower response rate in patients infected with ticarcillin-resistant strains is significant.

Introduction

Clavulanic acid, a potent inhibitor of bacterial β-lactamases, prevents destruction of penicillins by β-lactamase-producing organisms (Hunter *et al.*, 1980; Neu & Fu, 1978). The addition of clavulanic acid extends the spectrum of ticarcillin to include β-lactamase-producing strains of *Staphylococcus aureus*, Enterobacteriaceae, Gram-negative anaerobic rods, *Haemophilus influenzae* and some strains of *Pseudomonas aeruginosa* (Casey & Glauser, 1983; Lamothe, Auger & Lacroix, 1984; Fuchs *et al.*, 1984; Barry *et al.*, 1984; Clarke & Zemcov, 1984; Hunter *et al.*, 1980). The availability of an intravenous formulation of ticarcillin plus clavulanic acid (Timentin) prompted its clinical trial in the treatment of severe hospital infections.

Materials and methods

In-patients at the Centre Hospitalier Universitaire Vaudois, Lausanne, who required broad-spectrum antibiotic therapy for severe infections were eligible for inclusion in the

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study. Patients excluded were those with penicillin hypersensitivity, pregnant women, and patients who had received antimicrobials within the previous 72 h, unless those antimicrobials had proved ineffective.

Timentin was administered intravenously. Patients with normal renal function received 3·2 g (3 g ticarcillin + 0·2 g clavulanic acid) 4-hourly (7 patients) or 6-hourly (28 patients), or 5·2 g (5 g ticarcillin + 0·2 g clavulanic acid) 6-hourly (22 patients). The patients with renal failure received 3·2 g bd, 1·6 g (1·5 g ticarcillin + 0·1 g clavulanic acid) bd, 5·2 g bd, or 2·6 g (2·5 g ticarcillin + 0·1 g clavulanic acid) tds (one patient each dosage). The duration of treatment varied from 2–45 days (mean 12·5 days). Six patients were treated for less than five days either because a side effect (one case) or primary bacterial resistance (five cases) prompted a change of antimicrobial.

Samples of blood and appropriate specimens were collected for culture and susceptibility testing within two days before, and two to five days after commencement of therapy as well as two or three days and one or two weeks after the end of therapy (four weeks for urinary tract infections). Organisms were considered pathogenic if they grew from an appropriate specimen in an appropriate number and if the clinical setting was consistent. Disc diffusion susceptibility testing was performed as proposed by Fuchs *et al.* (1984).

Blood and urine specimens were drawn for haematological and biochemical investigations before the start of therapy, then at five-day intervals and at the end of therapy. Granulocytopenia was defined as less than 100 neutrophils per μl of blood.

Classification of responses to treatment

Clinical response. Patients were considered as clinically cured when clinical abnormalities subsided with no evidence of infection when the drug was discontinued or during follow-up; as improved when clinical abnormalities definitely diminished but with incomplete resolution of infection. Clinical failure was defined as no (or only transient) response to therapy. Patients were thought unassessable when they received concurrent appropriate antibiotherapy (with the exception of leukopenic patients receiving Timentin plus amikacin), or when Timentin was replaced at an early stage by other antimicrobials because of either Timentin resistance of the primary pathogen, or because of serious Timentin side effects.

The bacteriological response was classified as follows: eradication when the cultures from the original site of infection became negative; cure when clinical improvement was such that culture material was no longer available; failure when one or more culture sites remained positive for the same organism; relapse when, after becoming initially negative, cultures again grew the same organism; and reinfection when cultures showed secondary growth of another organism.

Results

Sixty-four episodes were studied in 62 patients. There were 41 males and 21 females, aged from 18 to 85 years (mean 50·5). A large number of associated conditions were present, as shown in Tables II to VIII.

Patient data are detailed in Tables II to VIII and summarized in Table IX. Overall, clinical cure or improvement were achieved in 59% and 14% respectively of the

Table I. Results of susceptibility testing of Timentin and ticarcillin[a]

Organisms	No. of isolates	No. of isolates susceptible to: Timentin and ticarcillin	Timentin but not ticarcillin	Neither Timentin nor ticarcillin
E. coli	13	10	3	
P. aeruginosa	13	10	1	2
Klebsiella spp.	5		4	1
Proteus spp.	5	5		
Morganella morganii	5	4	1	
Other Gram-negative rods[b]	4	2		2
S. aureus	7	2	5	
Other Gram-positive cocci[c]	9	9		
Anaerobic bacteria[d]	9	8	1	
Totals	70	50	15	5

[a]Performed by agar diffusion, or broth dilution for anaerobic isolates.
[b]*C. freundii* (1), *Ent. cloacae* (1), *P. cepacia* (1), *Aeromonas hydrophila* (1).
[c]*S. epidermidis* (1), Group D, streptococci (5), *Str. milleri* (2), Group A streptococcus (1).
[d]*Bacteroides fragilis* (1), *B. ruminicola* (1), *B. melaninogenicus* (2), *B. oralis* (1), *B. thetaiotaomicron* (1), *Peptococcus* species (2), *Eubacterium lentum* (1).

episodes. Thus, response to treatment occurred in 73% of the cases. There were 11 failures, while outcome could not be assessed in six cases.

Twenty-one episodes were not bacteriologically proved (of which 13 were fever in leukopenic patients). Among the 43 proved episodes, 25 were thought to be caused by one isolate, nine by two isolates and nine by three isolates. Thus 70 isolates were tested for ticarcillin and Timentin susceptibility (Table I). In five cases infection was caused by a pathogen found to be resistant to Timentin before Timentin administration. In five further cases a Timentin-resistant isolate appeared during treatment. Two patients had a reinfection with Timentin-resistant *Escherichia coli* and *Klebsiella pneumoniae*, and this resulted in failure. In three patients Timentin-resistant *Citrobacter freundii*, *Enterobacter cloacae* and *P. aeruginosa* respectively appeared after a corresponding Timentin-susceptible strain had been cultivated before treatment. This resulted in failure in two patients, while one patient was cured with concurrent gentamicin therapy to which the organism was susceptible. Of the 26 episodes caused exclusively by isolates susceptible to both Timentin and ticarcillin, 18 (69%) responded, five failed and two were unassessable. In contrast, of the 11 episodes caused by at least one strain susceptible to Timentin but resistant to ticarcillin, five (45%) responded, four failed and two were unassessable.

Adverse events

Three patients had side-effects severe enough to stop Timentin therapy. In one patient severe haematuria was accompanied by a prolonged bleeding time and impairment of ADP-induced platelet aggregation. Another patient developed pancreatitis without having any of the risk factors known to be associated with this condition. In both patients the problems resolved after Timentin withdrawal. One cirrhotic patient had a marked weight increase attributed to sodium overload secondary to Timentin administration. Several less serious adverse events were also attributed to Timentin:

Table II. Respiratory infections—pathogens and results of treatment with Timentin

Patient	Age	Sex	Diagnosis/underlying conditions	Pathogens/sensitivities to ticarcillin/Timentin	Outcome clinical	Outcome bacteriological	Remarks
1	53	M	Pneumonia/acute respiratory distress syndrome	*E. coli* (S/S)	cured	cured	
2	48	M	Pulmonary abscess/alcoholism	*Peptococcus* sp. (S/S) *B. ruminicola* (S/S) *B. melaninogenicus* (S/S)	cured	cured	Organisms isolated from metastatic foot abscess
3	55	M	Pneumonia/laryngeal carcinoma	*K. pneumoniae* (R/S)*	cured	eradicated	
4	61	M	Pneumonia/oesophageal carcinoma/alcoholism	*K. oxytoca* (R/S)	cured	cured	
5	54	M	Pneumonia/bronchial aspiration chronic obstructive pulmonary disease	no growth	cured	unassessable	
6	77	M	Pneumonia/metastatic oesophageal carcinoma	no growth	cured	unassessable	
7	46	M	Pneumonia/lobectomy for atypical mycobacteriosis	no growth	improved	unassessable	Concurrent multiple drug therapy for mycobacteriosis
8	55	M	Pneumonia/post-traumatic tetraplegia	no growth	improved	unassessable	
9	20	M	Pneumonia/multiple injuries	*P. aeruginosa* (S/S) *S. aureus* (S/S)	unassessable	unassessable	Gentamicin added. Healed despite Timentin-resistant *P. aeruginosa*
10	71	M	Pneumonia + empyema/open heart surgery 1 month previously	*S. aureus* (R/S)* *Ent. cloacae* (S/S)* *M. morganii* (S/S)	failure	failure	Concurrent tobramycin therapy. Developed Timentin-resistant *Ent. cloacae* sternotomy infection. Died of heart failure

*Blood culture isolate.

Table III. Ear, nose and throat infections—pathogens and results of treatment with Timentin

Patient	Age	Sex	Diagnosis/underlying conditions	Pathogens/sensitivities to ticarcillin/Timentin	Outcome clinical	Outcome bacteriological	Remarks
11	41	F	Relapse of chronic otitis media	*P. aeruginosa* (S/S)	cured	eradicated	
12	32	M	Relapse of chronic otitis media	*Pr. mirabilis* (S/S)	cured	eradicated	
13	43	M	External otitis/diabetes	*Pr. mirabilis* (S/S)	cured	eradicated	
14	31	M	Sinusitis/ethmoid carcinoma	*S. aureus* (R/S)	cured	eradicated	
15	50	M	Abscesses of floor of mouth, chronic obstructive pulmonary disease, alcoholism, cirrhosis	*B. melaninogenicus* (S/S) *Eu. lentum* (S/S)	cured	cured	
16	58	F	Pharyngeal abscess/metastatic breast carcinoma	*B. oralis* (S/S) *Peptostreptococcus* sp. (S/S)*	cured	eradicated	Due to antitumour chemotherapy, agranulocytosis developed after the start of Timentin therapy
17	26	M	Cheek abscesses/dental extraction	*S. milleri* (S/S)	cured	cured	
18	35	M	Tongue abscess/chronic obstructive pulmonary disease/alcoholism	no growth	cured	unassessable	
19	44	M	Postoperative rigors and fever/ Tongue carcinoma/chronic obstructive pulmonary disease/ alcoholism	no growth	cured	unassessable	Fever occurred during perioperative amoxycillin prophylaxis
20	48	M	Extensive surgery for relapse of laryngeal carcinoma	*A. hydrophilia* (R/R)*	failure	failure	Changed to ceftriaxone after 4 days Timentin

*Blood culture isolates.

Table IV. Skin and soft tissue infections—pathogens and results of treatment with Timentin

Patient	Age	Sex	Diagnosis/underlying conditions	Pathogens/sensitivities to ticarcillin/Timentin	Outcome clinical	Outcome bacteriological	Remarks
21	21	M	Cellulitis/traumatic rectal wound	*E. coli* (S/S)* *Str. faecalis* (S/S) *B. fragilis* (S/S)*	cured	eradicated	
22	28	F	Postoperative wound infection/obesity	*P. aeruginosa* (S/S)	cured	eradicated	
23	73	M	Donor graft site infection/laryngeal carcinoma	*Str. pyogenes* (S/S)* *S. aureus* (S/S) *P. aeruginosa* (S/S)	cured	eradicated	
24	53	M	Septicaemia after anal surgery/cirrhosis (alcohol)	*E. coli* (S/S)*	unassessable	unassessable	Timentin stopped after 3 days (sodium overload)
25	24	F	Cellulitis/extensive burns	*P. aeruginosa* (R/S)* *S. aureus* (R/S)* *K. pneumoniae* (R/S)	unassessable	unassessable	Concurrent amikacin and vancomycin therapy
26	18	M	Cellulitis/multiple injuries and surgery for fractured femur	*S. epidermidis* (S/S)	failure	failure	
27	54	M	Buttock abscess with rectal fistula/diabetes, severe cachexia	*E. coli* (S/S) *M. morganii* (S/S) *S. faecalis* (S/S)	failure	failure	Timentin-resistant *E. coli* appeared during therapy
28	84	F	Cellulitis, operated cutaneous carcinoma, cachexia	*S. aureus* (R/S) *M. morganii* (R/S)	failure	failure	Died after 5 days (probably cardiac)
29	62	F	Abdominal wall cellulitis/diabetes, renal failure, tetraplegia	*S. milleri* (S/S)*	failure	reinfected	Died after 15 days therapy despite surgical drainage (*B. fragilis* (R/S) isolated from pus during therapy)

*Blood culture isolate.

Table V. Urinary tract infections—pathogens and results of treatment with Timentin

Patient	Age	Sex	Diagnosis/underlying conditions	Pathogens/sensitivities to ticarcillin/Timentin	Outcome clinical	Outcome bacteriological	Remarks
30	55	F	Pyelonephritis/ureteric stone, diabetes	*Pr. mirabilis* (S/S)*	cured	eradicated	Stone removed endoscopically. Antibiotic treatment completed orally
31	60	M	Pyelonephritis/diabetes, obstructive nephropathy, cardiac failure	*P. aeruginosa* (S/S)	cured	eradicated	Severe haematuria: ticarcillin-induced platelet dysfunction
32	23	M	Pyelonephritis/urethral catheterization	*E. coli* (S/S)	cured	eradicated	Antibiotic treatment completed orally
33	30	F	Pyelonephritis/diabetes, medullary sponge kidneys	*E. coli* (S/S)	cured	eradicated	Antibiotic treatment completed orally
34	40	F	Urosepsis/chronic obstructive pulmonary disease	*E. coli* (R/S)*	cured	eradicated	Antibiotic treatment completed orally
35	78	F	Pyelonephritis/renal stone	*E. coli* (S/S)*	improved	eradicated	Antibiotic treatment completed orally
36	75	M	Urosepsis/cardiac failure, hip prothesis, urethral catheterization	*P. aeruginosa* (S/S)*	failure	unassessable	Timentin replaced by piperacillin. Gentamicin added to prevent hip infection

*Blood culture isolate.

Table VI. Bone infections—pathogens and results of treatment with Timentin

Patient	Age	Sex	Diagnosis/underlying conditions	Pathogens/sensitivities to ticarcillin/Timentin	Outcome clinical	Outcome bacteriological	Remarks
37	85	M	Osteomyelitis/cardiac and renal failure	*P. aeruginosa* (S/S) *Str. faecalis* (S/S)	cured	eradicated	
38	67	M	Diabetic foot with osteomyelitis	*Str. faecalis* (S/S) *Pr. vulgaris* (S/S) *M. morganii* (S/S)	improved	relapse	Antibiotic treatment completed orally
39	70	M	Diabetic foot with osteomyelitis/cardiac and renal failure	no growth	improved	unassessable	
40	49	F	Osteomyelitis	*P. aeruginosa* (S/S) *Str. faecalis* (S/S) *Pr. vulgaris* (S/S)	unassessable	unassessable	Concurrent aminoglycoside therapy
41	27	M	Osteomyelitis/pseudarthrosis	*P. aeruginosa* (R/R)	unassessable	unassessable	Timentin replaced by piperacillin. Concurrent aminoglycoside therapy
42	21	M	Osteomyelitis/pseudarthrosis	*P. aeruginosa* (S/S) *S. aureus* (R/S)	unassessable	unassessable	Concurrent aminoglycoside therapy

Table VII. Miscellaneous infections—pathogens and results of treatment with Timentin

Patient	Age	Sex	Diagnosis/underlying conditions	Pathogens/sensitivities to ticarcillin/Timentin	Outcome clinical	Outcome bacteriological	Remarks
43	51	M	Blind loop infection/pancreatic carcinoma	*E. coli* (S/S)* *K. pneumoniae* (R/R)*	improved	failure	Eventually cured after surgery and administration of ceftriaxone
44	64	M	Perforated diverticulitis with peritonitis/chronic obstructive pulmonary disease, renal failure	*E. coli* (S/S) *M. morganii* (S/S) *P. aeruginosa* (S/S)	failure	reinfected	Died from septicaemia due to Timentin-resistant *K. pneumoniae*
45	76	F	Peritonitis, suture leak after duodenal surgery/diabetes, cardiac failure	*C. freundii* (S/S) *K. pneumoniae* (R/S)	failure	failure	Development of Timentin-resistant *C. freundii*. Died from gastric haemorrhage
46	27	M	Clinical relapse one day after stopping therapy for *H. parainfluenzae* meningitis due to chronic otitis with cholesteatoma	no growth	cured	unassessable	
47	27	F	Bilateral pyosalpinx	*E. coli* (R/S) *B. thetaiotaomicron* (R/S)	cured	cured	Surgical drainage performed

*Blood culture isolate.

Table VIII. Febrile neutropenic patients—pathogens and results of treatment with Timentin and aminoglycoside

Patient	Age	Sex	Diagnosis/underlying conditions	Pathogens/sensitivities to ticarcillin/Timentin	Outcome clinical	Outcome bacteriological	Remarks
48	66	M	Acute myelogenous leukaemia	no growth	cured	unassessable	
49	49	M	Acute myelogenous leukaemia	no growth	cured	unassessable	
50	29	F	Hodgkin's disease	no growth	cured	unassessable	
51	60	M	Non-Hodgkin lymphoma	no growth	cured	unassessable	
52	35	M	Testicular carcinoma	no growth	cured	unassessable	
53	47	F	Ovarian carcinoma	no growth	cured	unassessable	
54	72	F	Acute myelogenous leukaemia	no growth	cured	unassessable	Concurrent herpes infection.
55	72	F	Acute myelogenous leukaemia	no growth	cured	unassessable	
56	71	F	X-lymphogranulomatosis, heart failure	no growth	cured	unassessable	Died from cerebral haemorrhage.
57	19	M	Acute myelogenous leukaemia	no growth	cured	unassessable	
58	54	F	Cefacetrile-induced agranulocytosis	no growth	cured	unassessable	
59	50	M	Acute myelogenous leukaemia	no growth	improved	unassessable	Died from overwhelming leukaemia
60	51	M	Non-Hodgkin lymphoma	no growth	failure	unassessable	Died in shock, possibly of septic origin
61	75	F	Acute lymphoblastic leukaemia	*E. coli* (S/S)*	cured	eradicated	
62	63	F	Acute myelogenous leukaemia	*P. cepacia* (R/R)*	improved	eradicated	Improvement despite amikacin resistance. Changed to ceftriaxone
63	52	F	IgA myeloma	*P. aeruginosa* (R/R)*	improved	unassessable	Timentin replaced by piperacillin
64	49	M	Acute myelogenous leukaemia	*E. coli* (R/S)*	failure	failure	*E. coli* isolated from blood 5 days after initiation of therapy

* Blood culture isolate.

Table IX. Clinical outcome of 64 episodes treated with Timentin

Localization	Number of episodes		Clinical outcome			
	total	microbiologically proved (Bacteraemia)	cure[a]	improved[a]	failure	unassessable[b]
Lower respiratory tract: pneumonia	10	6 (2)	6 (4)	2	1	1
Upper respiratory tract: E-N-T	10	8 (2)	9 (7)		1	
Soft-tissue	9	9 (5)	3 (3)		4	2
Complicated UTI	7	7 (4)	5 (5)	1 (1)	1	
Bone	6	5 (0)	1 (1)	2 (1)		3
Intra-abdominal	3	3 (1)		1	2	
Meningitis	1	0 (0)	1			
Pelvic	1	1 (0)	1 (1)			
Fever in neutropenic patients	13	0 (0)	11	1	1	
Septicaemia in neutropenic patients	4	4 (4)	1 (1)	2	1	
Total	64	43 (18)	38 (22)	9 (2)	11	6

[a] Numbers of bacteriological eradication plus cure are shown in parentheses.
[b] Because of concurrent therapy, or very early discontinuation of Timentin therapy due to adverse event, or primary resistance of pathogen.

catheter related phlebitis (10), minor changes in liver function tests (4), eosinophilia (2), and thrombocytopenia (1). A positive direct Coombs test developed in seven of 25 patients tested but there was no evidence of haemolysis. Skin rash and diarrhoea were not observed.

Discussion

This study demonstrates the clinical efficacy of Timentin against severe infections occurring in debilitated patients and due to a wide range of pathogens. However, the response rate (73%) is lower than that found in other clinical trials of Timentin (File *et al.*, 1984; Roselle *et al.*, 1985). In our study, failure mainly occurred in abdominal and soft tissue infections in patients with severe underlying conditions which clearly represented a difficult challenge to antibiotic therapy. Other authors have observed apparently discrepant response rates with other antibiotics such as ceftazidime (Francioli *et al.*, 1983; Hoogkamp-Korstanje, van Erpecum & van Kamp, 1985), and ascribed them to differences in the numbers of patients with serious underlying conditions (Hoogkamp-Korstanje *et al.* 1985).

The appearance of Timentin-resistant isolates may explain some of our treatment failures. In five instances a resistant pathogen appeared during therapy, resulting in four failures; one case was unassessable because of concurrent therapy. In five instances infection was caused by a pathogen found to be resistant to Timentin before Timentin administration. This incidence of Timentin resistance among primary pathogens contrasts with previous findings at our institution. Among 404 blood cultures isolated between 1979 and 1981, only five *P. aeruginosa* were found not to be inhibited by 32 mg/l ticarcillin in the presence of 5 mg/l clavulanic acid (Casey & Glauser, 1983). Although our study population was selected for severe disease caused by multiresistant organisms, these figures may suggest that Timentin resistance is becoming more common in our hospital and it can now be observed in species other than *P. aeruginosa*. The frequent occurrence of mixed infections precluded an analysis of the efficacy of Timentin with respect to the infecting species. However, our data indicate that clavulanic acid did not restore ticarcillin activity against most ticarcillin-resistant *P. aeruginosa*, thus confirming previous reports (Casey & Glauser, 1983; Fuchs *et al.*, 1984; Barry *et al.*, 1984).

The somewhat lower response rate in patients infected with ticarcillin-resistant but Timentin-susceptible strains, when compared to patients infected by strains susceptible to both antibiotics, is conspicuous but difficult to interpret because the two groups were not comparable, making the significance of the difference questionable.

Timentin was generally well tolerated. Two patients had severe adverse events which could be explained solely on the basis of the known properties of ticarcillin, i.e. a ticarcillin-induced platelet function impairment (Bang & Kammer, 1983), and a water-sodium overload. In one case there was a questionable relationship between Timentin therapy and the development of pancreatitis. In no other instances did an adverse event make discontinuation of Timentin necessary. The high proportion of positive Coombs tests was not unexpected, having been reported by Williams *et al.* (1985). It is caused by clavulanic acid-mediated non-immune adsorption of plasma proteins on the erythrocyte surface, a phenomenon unassociated with haemolysis.

In summary, Timentin proved to be a safe and effective broad-spectrum agent for the treatment of severe hospital infections. However, development of resistance during

therapy or reinfection with resistant organisms are a matter of concern, and the need to add an aminoglycoside to Timentin in these settings should be explored.

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