



**HAL**  
open science

## Severe coagulation disorder with hypofibrinogenemia associated with the use of tigecycline

Herwig Pieringer, Bernhard Schmekal, Georg Biesenbach, Erich Pohanka

► **To cite this version:**

Herwig Pieringer, Bernhard Schmekal, Georg Biesenbach, Erich Pohanka. Severe coagulation disorder with hypofibrinogenemia associated with the use of tigecycline. *Annals of Hematology*, 2010, 89 (10), pp.1063-1064. 10.1007/s00277-010-0911-7. hal-00510832

**HAL Id: hal-00510832**

**<https://hal.science/hal-00510832>**

Submitted on 22 Aug 2010

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Editorial Manager(tm) for Annals of Hematology  
Manuscript Draft

Manuscript Number: AOHE-D-09-00483R1

Title: Severe coagulation disorder with hypofibrinogenemia associated with the use of tigecycline

Article Type: Letter to the Editor

Keywords: tigecycline; hypofibrinogenemia; coagulation disorder

Corresponding Author: Dr. Herwig Pieringer,

Corresponding Author's Institution: General Hospital Linz

First Author: Herwig Pieringer

Order of Authors: Herwig Pieringer; Bernhard Schmekal; Georg Biesenbach; Erich Pohanka

Abstract: Letter

Response to Reviewers: 1. As the authors correctly pointed out, tigecycline is already known to induce a slight increase of PTT and PT (sec). The mean increase of PTT was around 5 seconds in the studies listed in the FDA medical report. An increased bleeding risk could not be observed. The FDA speculated two mechanisms for the coagulation abnormalities: Vit K deficiency and hypoproteinemia. The first reason can be excluded (the patient repeatedly received Vit K), the second reason should be addressed in the letter. However, only one out of 71 reported hypoproteinemia was categorised as serious.

Reply:

The medical review (assessed from [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2005/21-821\\_Tygacil\\_Medr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21-821_Tygacil_Medr.pdf)) mentions "Vitamin K deficiency" and "direct drug effects on the clotting cascade" as possible explanations. "Hypoproteinemia" is mentioned a few lines above that paragraph. All these aspects have been briefly summarized in the revised paper. The appropriate reference has been given.

2. The time course of onset and withdrawal of the other medications (carbapenem/cilastin and anidulafungin) is not accurately described in the manuscript. The time course of lab results and medications might be presented in a figure or table. The figure or table should also include time course of platelet count and D-Dimer (see below).

Reply:

The duration of treatment for carbapenem/cilastin and anidulafungin has been added. We included a table of lab results (a figure would be confusing because of the varying scales of the different parameters).

3. In the light of the already known effects on coagulation tests, the absence of thrombocytopenia and the absence of a clinical picture compatible with a microthrombotic disorder, the supposed diagnosis "DIC" is questionable, although I have no other ready diagnosis. Primary hyperfibrinolysis would not be associated with AT-deficiency and a transient inhibitor can also not explain the findings. First, it would be of great interest to know if D-Dimer increased at the time when the coagulation

abnormalities occurred. This would imply a process which is truly associated with hyperfibrinolysis rather than impaired synthesis. Second, because the criteria for DIC are not fulfilled the authors might avoid the diagnosis DIC and apply a descriptive term such as "severe coagulation disturbance".

Reply:

We agree that the diagnosis "DIC" is questionable. We discussed this in the original version of the manuscript and we also stated why we did not rely on this diagnosis. However, in such a situation one might consider "DIC" as a differential diagnosis, even if criteria are truly not fulfilled. Therefore, we have modified this paragraph in the following way:

"These changes are in line with a severe coagulation disturbance, which has also some of the characteristics of disseminated intravascular coagulation, a condition which might develop in a patient with severe peritonitis. However, there was a certain level of distrust since the coagulation disorder became more severe while signs of inflammation improved. In addition, platelets remained within the normal range, the patient did not demonstrate any signs of end-organ damage due to microthrombosis nor was there evidence of bleeding."

Unfortunately, the time course of D-Dimer cannot be answered retrospectively as we do not have enough measurements (we do only have a measurement 1 day before the 14.18 mg/l: this was 6.75 - we do not feel that this is sufficient for a final statement on that point). This also relates to comment 2 (no time course of the D-Dimer in the table).

4. The statement of a "very likely" association should be attenuated (page 2, line 9).

Reply:

This has been done.

**\*Conflict of interest**

**[Click here to download Conflict of interest: Conflict of interest.doc](#)**

**Severe coagulation disorder with hypofibrinogenemia associated  
with the use of tigecycline**

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Herwig Pieringer, Bernhard Schmekal, Georg Biesenbach, Erich Pohanka

2<sup>nd</sup> Department of Medicine  
Section of Nephrology  
Krankenhausstr. 9  
General Hospital Linz  
A-4020 Linz

Contact to: [herwigpi@yahoo.com](mailto:herwigpi@yahoo.com)  
Tel: +43/732/7806-6310  
Fax: +43/732/780-6135

Dear Editor,

Tigecycline is an expanded broad spectrum antibiotic used to treat complicated skin infections or complicated intra-abdominal infections [1]. We report a case in which the use of tigecycline was associated with a severe coagulation disorder, which resolved rapidly and completely after discontinuing the drug.

A 54 year old female patient with endstage renal disease (ESRD) undergoing continuous ambulatory peritoneal dialysis contracted a second episode of peritonitis (*E. coli*, *Klebsiella oxytoca* and *Candida albicans*). Markers of systemic inflammation were markedly elevated (white blood cell count 19.3 G/l, C-reactive protein 34.1 mg/dl). The patient was in a reduced general condition. Imaging studies failed to demonstrate an intestinal perforation. The initial anti-infective regime consisted of imipenem/cilastin and fluconazole. The peritoneal catheter was removed and the patient was switched to hemodialysis. However, the peritonitis did not improve. Therefore, diflucan was switched to anidulafungin and tigecycline was added. Of note, the patient did not have an underlying hepatic disease [2]. Consecutively, signs of systemic inflammation and the patient's condition improved. Therefore, carbapenem/cilastin (after 29 days) and anidulafungin (after 27 days) were stopped, tigecycline was continued (overlap with the other two anti-infective agents for about 3 weeks). However, imaging studies revealed the formation of an intraabdominal abscess which was partially drained under computed tomography guidance. During the course a slow, but progressive deterioration of coagulation parameters was noted (International Normalized Ratio increased to 3.08, activated partial thromboplastin time [aPTT] raised from 30.5 to >160 sec; normal range [NR]: 23.0-31.9 sec). These changes were refractory to vitamin K supplementation. In addition, there were high levels of D-dimer (14.18 mg/l; NR: 0-0.5mg/l), reduced levels of antithrombin III (AT III) (28%; NR: 75-125%) and severe hypofibrinogenemia (28mg/dl; NR: 180-400mg/dl). These changes are in line with a severe coagulation disturbance, which has also some of the characteristics of disseminated intravascular coagulation, a condition which might develop in a patient with severe peritonitis [3]. However, there was a certain level of distrust since the coagulation disorder became more severe while signs of inflammation improved. In addition, platelets remained within the

1 normal range, the patient did not demonstrate any signs of end-organ damage due to  
2 microthrombosis nor was there evidence of bleeding.  
3  
4

5 As we suspected an association with the prolonged use of tigecycline we  
6 discontinued the drug despite the abscess. From the next day on aPTT (normalized  
7 within 6 days), AT III (37% after 4 days) and fibrinogen improved markedly  
8 (normalized within 5 days). The strong time-dependent association of the coagulation  
9 disorder and the prolonged use of tigecycline and its reversal after discontinuation  
10 (table 1) might point to a causative role of the drug. Previously, a prolonged aPTT  
11 during treatment with tigecycline was noted [2]. The FDA mentions vitamin K  
12 deficiency due to the effects on the flora of the intestine as one of the possible  
13 mechanism [4]. This can be excluded in the given case as the patient received  
14 vitamin K supplementation. Further speculated mechanisms are direct drug effects  
15 on the clotting cascade and drug related hypoproteinemia. It is recommended to  
16 monitor aPTT in patients receiving warfarin and tigecycline [2, 5]. However, to date  
17 no case has been reported, in which there was life-threatening hypofibrinogenemia  
18 and prolongation of aPTT and INR. Whether the patient's ESRD and/or the long  
19 treatment duration (total of 39 days) may have influenced the results remains open.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

33  
34 In conclusion, we believe that monitoring INR, aPTT and fibrinogen should be  
35 considered in all patients receiving tigecycline, especially if the treatment will last for  
36 a longer duration. If patients do develop hypofibrinogenemia one should consider  
37 stopping tigecycline.  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

References:

1. Pankey GA. Tigecycline. *J Antimicrob Chemother.* 2005;56:470-80
2. <http://www.wyeth.com/content/getfile.asp?id=491> (assessed 01 MAY 2009)
3. Egi M, Morimatsu H, Wiedermann C, Tani M, Kanazawa T, Suzuki S, Matsusaki T, Shimizu K, Toda Y, Iwasaki T, Morita K. Non-overt disseminated intravascular coagulation scoring for critically ill patients: The impact of antithrombin levels. *Thromb Haemost* 2009; 101: 696–705
4. [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2005/21-821\\_Tygacil\\_Medr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21-821_Tygacil_Medr.pdf)
5. Zimmerman JJ, Raible DG, Harper DM, Matschke K, Speth JL. Evaluation of a potential tigecycline-warfarin drug interaction. *Pharmacotherapy.* 2008;28:895-905

