Drug-induced disseminated intravascular coagulation: a pharmacovigilance study on World Health Organization's database

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Running head: Drug-induced intravascular coagulation

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Abstract.

Background: Disseminated intravascular coagulation (DIC) occurs in several clinical conditions, including drug therapy. We aim to investigate the association between several drug classes use and DIC onset, using the reports of Adverse Drug Reactions (ADR) collected in Vigibase, the World Health Organization database of ADR.

Methods: We collected reports of drug-related DIC from 1968 to September 2015 and classified in VigiBase according to the MedDRA (Medical Dictionary for Regulatory Activities) term "Disseminated intravascular coagulation". A disproportionality analysis using Reporting Odds Ratio (ROR) was performed.

Results: Overall 4653 reports of drug-associated DIC were selected, 75.9% was serious. DIC was significantly (ROR > 1) associated with 88 drugs, mainly antineoplastic agents, antithrombotic agents and antibacterials for systemic use. Among of the most frequently reported individual drugs were dabigatran (94 reports) ROR = 1.34 (1.08 – 1.67), oxaliplatin and bevacizumab both with 75 reports and ROR = 1.77 (1.38 – 2.27) and 2.02 (1.57 – 2.61), respectively.

Conclusion: A considerable number of drugs widely used in the population may be associated with the potential occurrence of DIC. For many of these, the ADR is not listed. The high number of drugs involved underline the importance of evaluate this condition such as an ADR that might occur during therapy.

Keywords: Adverse Drug Reactions, Disseminated Intravascular Coagulation, Drug Safety, Pharmacovigilance.

23 **Keypoints**

24 1. The evaluation of possible drug-induced serious syndromes is important to
25 guarantee the patients' safety.
26 2. A high number of drugs widely used in the population may be associated with
27 rare and serious adverse drug reactions.
28 3. Clinicians should be aware of the importance to identify and report every case of
29 suspected drug – related disseminated intravascular coagulation.
30 4. The assessment of the association between the drug and the adverse drug
31 reaction may result in the updating of the summary of product characteristics.
32 5. Early detection of possible drug-induced disseminated intravascular coagulation
33 makes management easier by the possible suspension of the suspect drug.
34

Introduction

Blood coagulation is a physiological process put in place by the body during particular conditions; blood has to preserve its fluidity within vascular system but at the same time should be able to coagulate when exposed to non – endothelial surface in vascular lesion site and also to reset its normal flow after coagulation, through fibrinolysis [1]. Dysregulation of the homeostatic pathways results in changes that may affect preponderance of fibrinolysis or blood coagulation. Disseminated intravascular coagulation consists in the co-occurrence of both these components. Half a century ago, disseminated intravascular coagulation wasn't known and during autopsy it was almost impossible to find evidence of vascular disorders. Only at the end of the 1970s, more was known about it and, in addition, Sparo and colleagues [2] defined the acronym DIC as "Death Is Coming", underlying the impact that this condition has on patients' life. DIC is a rare and serious syndrome characterized by the wide activation of coagulation process resulting in fibrin formation and consequent thrombosis of small to medium vessels [3]. At the same time, depletion of coagulation proteins and platelets brings to severe bleeding. Recent studies clarified the pathogenetic pathway of the syndrome that seems to be caused by activation of pro inflammatory cytokines, that along with suppression of anticoagulation pathway, culminate to generation of thrombin. This activation takes place from interlukin-6 (IL-6) and, indirectly, from tumor necrosis factor alfa through its influences in IL-6 activation [4]. DIC may result as a complication of serious infection such as sepsis, severe trauma, vascular disorders, obstetrical complications, toxins or cancer. Last but not least, DIC could be also considered as an adverse drug reaction (ADR) although in literature there are very few evidences in this regard [5,6]. To the best of our knowledge, no previous studies have analyzed reports of ADRs related to DIC deriving from spontaneous reporting system.

We aimed to investigate the potential association gathered from the use of several drug classes and the onset of DIC in order to improve the knowledge about DIC as an ADR and to underline the drugs for which it should be considered. By analyzing WHO database of adverse drug reactions and through evaluation of international literature, we want to give an overview of a subject about which little is known to date.

Methods

This is a case-by-case evaluation of all the reports of disseminated intravascular coagulation reported in the Vigibase, the WHO Global Individual Case Safety Report (ICSR) database at the Uppsala Monitoring Centre. The center has received reports about individual suspected ADRs from the countries participating in the WHO Programme for International Drug Monitoring (PIDM) starting from 1968 [7]. We collected all the suspected DIC-related cases reported from 1968 to September 2015 and classified in VigiBase with the MedDRA (Medical Dictionary for Regulatory Activities) Preferred term level “disseminated intravascular coagulation” and “disseminated intravascular coagulation in newborn”. The MedDRA is a standardized medical terminology used worldwide and having a hierarchy structures in which all the ADRs are grouped in System Organ Class (SOC) by type and etiology. The maximum precision level is defined by the preferred term, which we used for the selection of our cases. Vaccines were excluded from this analysis. Only drugs reported as suspected or interacting were evaluated. Considering that more than one drug could be reported as suspected, we analyzed the reports by drug-reaction pairs and not by number of reports. We performed a duplicate chrck using a record-linkage strategy by grouping the overlapping records in 8 key fields: country-text, gender, age-reaction, re-outcome, preferred-base name, reported-term, onset date, and start date.

The records having 7 out of 8 overlapping information and a single missing data in the relevant key fields were considered as duplicates. We selected the drug – DIC pairs and we evaluated the disproportionality of these pairs compared to the others in the database. This analysis was performed using the Reporting Odds Ratio (ROR) with 95% confidence interval and p value ≤ 0.05. This is a quantitative approach based on frequency analysis of 2 x 2 contingency table, developed for evaluating drug – reaction frequency compared to reference distributions of other ones from the whole database [8]. If ROR < 1, it is assumed that we are in absence of disproportionality and the distribution of reported adverse events is the same across drugs [9]; conversely, if ROR is > 1 there is an increased frequency for the drug – reaction pair considered. Only drugs with the lower bound of the 95% CI > 1 were considered as related with the ADR considered. For each drug with a statistically significant ROR (ROR > 1, p value ≤ 0.05, lower bound 95% CI > 1), we verified if disseminated intravascular coagulation was reported in the Summary of Product Characteristics (SPCs) of the corresponding medicinal products, made available by the Italian Medicine Agency (AIFA), the European Medicines Agency (EMA) and the Electronic Medicines Compendium (eMC).

Results

Descriptive analysis

Analyzing reports from 1968 to December 2015 in Vigibase, we collected 4,771 Individual Case Safety Report (ICSR) referred to disseminated intravascular coagulation. After the exclusion of duplicates, 4,653 reports remained for the analysis (***Figure 1***). Focusing on these reports, 42.7% were related to 18 - 64 years patients, 29.9% to ≥ 65 years and 8.5% to 0 - 17 years. In about 19% of the cases, age was not available. Negligible difference emerged between females and males (51.2% and 45.1% respectively), while information about gender was not available in 3.7% of the reports. ***Table 1*** shows reports classified according to age class, number of reports (N) and gender for each class. About "seriousness" criteria, we applied ICSRs standards and out of 4653 reports, 75.9% was classified as serious, while only 1.25% was not serious. Seriousness was missing in 1066 (22.9%) reports. The highest number of serious cases on the total amount of reports per class was detected in ≥ 65 years class (1104 out of 1391, 79.4%). Considering "serious" cases, 1938 (54.9%) had a fatal outcome. Of these, 38.4% (697 of 1938) occurred in 18 – 64 years class, 36.0% (697 of 1938) in elderly and 7.6% (147 of 1938) in 0 – 17 years class. The mortality rate, calculated on the total number of reports per age class were: 36.8% in the 0 – 17 years class, 37.4% in the 18 – 64 years class and 50.1% in the elderly. ***Table 1*** also shows "seriousness" classification and fatal outcome for each class.

Disproportionality analysis

Out of the total number of reports collected in Vigibase, 4,653 reports were selected applying exclusions criteria (e.g.: all duplicates with same information such as origin, gender, age or suspected drugs). In these reports, 1,111 drugs were reported as

126 associated with DIC. Among these, 407 drugs have been excluded because reported
127 DIC only once and this was considered not enough to generate an alarm signal. The 704
128 remaining drugs were reported as suspected/interacting in more than one report related
129 to DIC. The top five drugs reported of 704 remaining were: heparin (184 reports),
130 methotrexate (143 reports), paracetamol (117 reports), vincristine (110 reports) and
131 cytarabine (108 reports). Eighty-eight drugs were statistically associated with DIC
132 (ROR > 1, 95% confidence interval and p value ≤ 0.05). Among these, the most
133 frequently reported was paracetamol (117 reports), ROR [1.21 (95% CI 1.00 – 1.48)],
134 followed by dabigatran (94 reports) ROR [1.34 (1.08 – 1.67)], oxaliplatin and
135 bevacizumab both with 75 reports, ROR [1.77(1.38 – 2.27)] and ROR [2.02 (1.57 –
136 2.61)] respectively. According to the ATC II level classification, the highest number of
137 drugs reported belong to antineoplastic agents (18 drugs), antithrombotic agents (12
138 drugs) and antibacterials for systemic use (10 drugs). Reports of antineoplastic agents
139 (L01, 593 reports) include oxaliplatin, bevacizumab, sunitinib ROR [1.58 (1.22 – 2.06)],
140 cisplatin ROR [1.72 (1.32 – 2.25)] and other 14 drugs; only for sunitinib DIC was an
141 ADR reported in SPC. As far as antithrombotic agents (B01, 290 reports), significant
142 RORs were observed for dabigatran, drotrecogin alfa ROR [2.05 (1.58 – 2.66)],
143 clopidogrel ROR [1.70 (1.24 – 2.32)], abiciximab ROR [2.21(1.35 – 3.62)] and other 8
144 drugs. For all these drugs, DIC was not reported in the SPCs. Other two classes with
145 high reporting frequency were N02 - analgesics (149 reports) and J01 - antibacterials for
146 systemic use (102 reports). *Table 2* shows the 88 drugs and the relative RORs; only 10
147 out of 88 have DIC listed in their SPCs: sunitinib, tegafur/gimeracil/oteracil, heribulin,
148 eptacog alfa, hetastarch, edaravone, rifampicin, quinine, acetylsalicylic acid and
149 dinoprostone.

150 **Discussion**

151 To the best of our knowledge, this is the first study concerning drug-induced DIC based
152 on data of spontaneous reporting collected from Vigibase. DIC is a rare syndrome and it
153 is even more infrequent as an ADR and evidences in literature are poor. Anyway, great
154 attention should be paid to this ADR because in the elderly, half of the reports of
155 adverse reactions, had a fatal outcome. The high DIC mortality rate strengths the need
156 to understand all the possible causes and to identify all the drugs associated to it, in
157 order to diagnose the ADR precociously. Overall, 88 drugs were statistically associated
158 with DIC, a great number if we consider that only for 10 of them the ADR is reported in
159 the corresponding SPC. For example, paracetamol shows a ROR > 1 in our analysis,
160 although the lower limit of the confidence interval was CIlow95%= 1.00. The
161 association paracetamol-DIC has been previously highlight by the Italian Medicine
162 Agency (AIFA) in three case reports of the December 2006 bulletin [10]. Paracetamol is
163 one of the most used drug worldwide, so it would be important to define clearly its
164 safety profile. Also oxaliplatin and bevacizumab were between the most reported drugs.
165 The class of antineoplastic agents deserves attention based on the several reports
166 identified (593). A statistically significant disproportionality has been obtained with
167 many drugs of the class such as oxaliplatin, bevacizumab, fluorouracil, irinotecan and
168 cetuximab. Literature provides evidences regarding a case report of DIC during third-
169 line treatment with cetuximab plus irinotecan, following 5-fluorouracil, leucovorin,
170 oxaliplatin (FOLFOX) plus bevacizumab and 5-fluorouracil, leucovorin and irinotecan
171 (FOLFIRI) plus bevacizumab [11] that is in accordance to our data. To note that DIC
172 could be also caused by tumor as well, both solid tumors and hematologic cancers [4],
173 and this makes the causality assessment complicated. Another high reported class were
174 antithrombotic/anticoagulant drugs (290 reports), in which we find a signal from the
175 association dabigatran – DIC. A recent published article concerning efficacy and safety

176 of direct oral anticoagulants is in agreement with our data: the association between
177 dabigatran and DIC has been classified as statistically significant and the author
178 explained that it was the suspected drug in about 90% of cases [8]. In dabigatran SPC it
179 is reported that it extends both prothrombin time and activated partial thromboplastin
180 time, as it happens in essential laboratory tests for DIC diagnosis. None report was
181 retrieved for other anticoagulants of the class such as rivaroxaban and apixaban. This
182 could be due to the higher use of dabigatran in clinical practice [12,13]. The third most
183 reported class was antibacterials agents for systemic use, but few evidences are present
184 in literature. In general, all these three classes are also the most used drugs for the
185 treatment of pathological conditions associated with the development of DIC. This
186 underlines the need to carry out further studies to better understand the etiology and the
187 possible causal association with the administration of the aforementioned drugs.
188 Anyway, confirmations to the data of our study is given from the 10 drugs resulted to be
189 associated with DIC, for which it is an ADR reported in the SPCs and confirmed by
190 findings in the literature. These include sunitinib, the combination
191 tegafur/gimeracil/oteracil, eribulin, hetastarch, rifampin, quinine, acetylsalicylic acid,
192 dinoprostone and edaravone. Overall, considering the high mortality rate, the large
193 number of reports retrieved and the confirmations deriving from drugs reports for which
194 DIC is already known, we can say that it would be appropriate to carry out further
195 analysis in order to obtain more confirmations to these possible associations identified.
196 Only with further studies, it will be possible to guarantee the updating of the SPCs and
197 ensure safer use of these drugs. Between the limitations of our study, stimulating
198 reporting or under reporting represents bias in the analysis. Underreporting widespread
199 and it is estimated that only the 10% of ADRs occurring in everyday clinical practice
200 are actually reported [14]. DIC underreporting could also be linked to doubts about the
201 causality role of drugs involved. In addition, clinical information in spontaneous reports

are limited and not completed, for example co-morbidities could not be reported. DIC could also be caused by trauma, sepsis or malignancy so it is important to know every clinical information about patients in order to assess the right causality. Furthermore, the preferred term “disseminated intravascular coagulation” is highly specific and not always clinicians should use this term for report DIC in ADR reports but may use other generic terms such as coagulopathy or hematological disorders, which cause a bias in entire following analysis. Inaccuracies in the initial evaluation of clinical condition could lead to an incorrect assessment. Lastly ROR computing does not allow to quantify the actual risk of an ADR but only suggests a statistically significant association between events and drugs. The indication of a statistically significant association must be confirmed and deepened by other epidemiological studies. Nevertheless, the spontaneous reporting remains one of the simplest, low cost and essential methods for identifying ADR during post-marketing surveillance.

Conclusion

The results of our analysis highlight that a considerable number of drugs widely used in clinical practice may be associated with the potential occurrence of DIC. For many of these, the ADR is not reported in the SPC and this may be a further obstacle for the identification. The high number of drugs involved, the few evidences in literature and the great number of fatal outcome underline the importance of evaluate this condition such as an ADR that might occur during therapy. Our study provides valuable data for further analysis and clinicians should be aware of the importance to identify and report every case of suspected drug – related DIC. Studies based on spontaneous reporting, even with limitations, allow to detected ADRs after marketing authorization and improve knowledge on the safety profile of many drugs.

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Figure Legend:

- **Figure 1: Flowchart of the Individual Case Safety Reports selection**