

Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

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THE US FOOD AND DRUG ADMINISTRATION (FDA) licensed recombinant human coagulation factor VIIa (rFVIIa) on March 25, 1999, for treatment of bleeding episodes in patients with hemophilia A or B and inhibitors to factor VIII or factor IX.¹ Recombinant FVIIa is structurally nearly identical to human plasma-derived coagulation factor VIIa and is thought to promote hemostasis by activating coagulation factors IX and X when complexed with tissue factor. Factor Xa, in a complex with factor V, calcium, and phospholipids, converts prothrombin to thrombin. Thrombin induces local hemostasis by converting fibrinogen to fibrin, which polymerizes and forms a thrombus in conjunction with platelets at the site of vascular injury. Thrombin can also be generated on the surface of activated platelets by the action of rFVIIa. Given the physiology of activated factor VII, a potential adverse event (AE) of concern is pathological clot formation.

The professional package insert for the US-licensed indication in hemophilia states that the risk of rFVIIa-associated thromboembolic AEs is not known but is thought to be low.¹ The package insert includes a warning section cautioning that thromboembolic risk may be increased in patients with disseminated intravascular coagulation, advanced atherosclerotic disease, crush injury, septicemia, or con-

Context The US Food and Drug Administration (FDA) licensed recombinant human coagulation factor VIIa (rFVIIa) on March 25, 1999, for bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX. Use in patients without hemophilia has been increasing since licensure.

Objective To review serious thromboembolic adverse events (AEs) reported to the FDA's Adverse Event Reporting System (AERS).

Design, Setting, and Patients The AERS database was reviewed from March 25, 1999, through December 31, 2004, for thromboembolic AE reports with rFVIIa. The AERS database includes US and non-US spontaneous AE reports from both approved (specific indications for patients with hemophilia) and unlabeled uses. It also includes serious AEs in patients enrolled in postlicensure clinical trials who received rFVIIa. Manufacturer reporting to FDA is mandatory, but primary notification from clinicians and others to FDA or manufacturers is voluntary for spontaneous reports; therefore, AERS underrepresents actual event occurrences.

Main Outcome Measure Reported thromboembolic events occurring in patients administered rFVIIa.

Results A total of 431 AE reports for rFVIIa were found, of which 168 reports described 185 thromboembolic events. Seventeen events occurred in patients with hemophilia and 59 occurred in patients enrolled in postlicensure trials. Unlabeled indications accounted for 151 of the reports, most with active bleeding (n=115). Reported AEs were thromboembolic cerebrovascular accident (n=39), acute myocardial infarction (n=34), other arterial thromboses (n=26), pulmonary embolism (n=32), other venous thromboses (including deep vein thrombosis) (n=42), and clotted devices (n=10). In 36 (72%) of 50 reported deaths, the probable cause of death was the thromboembolic event. In 144 patients with timing information, 73 events (52%) occurred in the first 24 hours after the last dose (30 events within 2 hours). Sixty-four reports (38%) noted concomitant use of hemostatic agents. Most reports lacked sufficient information to evaluate potential dosage associations.

Conclusions Most reported thromboembolic AEs followed the use of rFVIIa for unlabeled indications and occurred in arterial and venous systems, often resulting in serious morbidity and mortality. Analysis of the relationship between AEs and rFVIIa is hindered by concomitant medications, preexisting medical conditions, confounding by indication, and inherent limitations of passive surveillance. Randomized controlled trials are needed to establish the safety and efficacy of rFVIIa in patients without hemophilia.

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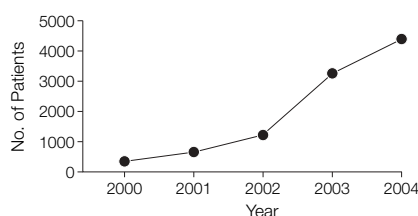
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comitant treatment with activated or nonactivated prothrombin complex concentrates, due to circulating tissue factor or predisposing coagulopathy.¹ The warning in the package insert revised recently (October 2005) includes information about thromboembolic AEs in patients without hemophilia.

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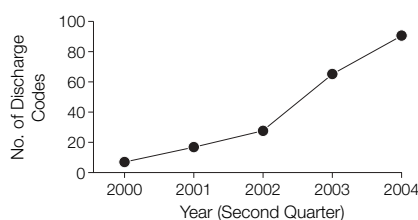
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Figure 1. Estimated Number of Patients Treated With Recombinant Human Coagulation Factor VIIa by Year



Estimations were based on Premier RxMarket Advisor (Premier Healthcare Informatics, Premier Inc, Charlotte, NC).

Figure 2. Unique ICD-9 Hospital Discharge Codes for Recombinant Human Coagulation Factor VIIa by Year



ICD-9 indicates *International Classification of Diseases, Ninth Revision*.⁵ Estimations were based on Premier RxMarket Advisor (Premier Healthcare Informatics, Premier Inc, Charlotte, NC).

The medical literature increasingly describes rFVIIa use in patients without hemophilia,² and use of rFVIIa has increased substantially in the United States. We reviewed thromboembolic AEs following administration of rFVIIa reported to FDA's Adverse Event Reporting System (AERS) database, also known as MedWatch.³ The AERS database is a passive surveillance system that receives AE reports from product manufacturers, health care professionals, and the public. Although reporting to FDA is required of manufacturers, primary reporting to the manufacturers or FDA by health care professionals and consumers is voluntary. The number of AEs received by FDA for a given product usually largely underestimates the actual number of occurrences. The extent of underreporting is unknown but is likely affected by numerous factors, including time

since a product's introduction to the market, publicity, and perceptions in the prescribing community regarding product safety and efficacy. Therefore, this case series does not provide incidence rates for thromboembolic AEs after use of rFVIIa. Case series usually cannot establish whether the relationship between a product and an event is causal or coincidental, because spontaneous reports have no controls, are subject to numerous potential reporting biases, and have other limitations.³ Despite these inherent limitations, spontaneous reports can contribute to the generation of hypotheses for further study and, with appropriate cautions for their interpretation, help inform physicians and patients of potential risks.

METHODS

We reviewed the AERS database from March 25, 1999, the approval date, through December 31, 2004, for thromboembolic AE reports with rFVIIa identified as a suspect product. We sought reports with the following standardized Medical Dictionary for Regulatory Activities international terminology codes: high level group term *embolism and thrombosis* and preferred terms *cerebrovascular accident*, *acute myocardial infarction*, and *myocardial infarction*. After medical review of the identified reports, thromboembolic AEs were grouped into the following mutually exclusive categories: cerebrovascular accidents, myocardial infarctions, other arterial thromboses, pulmonary embolism, other venous thromboses (including deep vein thrombosis), and clotted devices. Arteriovenous hemodialysis shunt thromboses were included in the clotted devices category. Disseminated intravascular coagulation cases were excluded from this case series, because except in 2 sepsis cases disseminated intravascular coagulation appeared to precede rFVIIa exposure.

The AERS database may include AE reports from a product's use in clinical practice or in postlicensure clinical trials. Adverse event ascertain-

ment is more complete in postlicensure trials because study clinicians must report certain AEs to the manufacturer,⁴ whereas clinician reporting outside of a trial is voluntary. In this review, spontaneous reports refer to patients who are not in a trial and trial reports refer to patients enrolled in postlicensure rFVIIa studies (AERS does not include AEs from prelicensure rFVIIa trials). In this case, all postlicensure trials involved patients who did not have hemophilia. Labeled use of rFVIIa refers to its utilization for indications within the US professional package insert as of December 31, 2004 (treatment of bleeding episodes in patients with hemophilia A or B and inhibitors to factor VIII or factor IX). Use for other purposes is off-label or unlabeled.

We used Premier RxMarket Advisor (Premier Healthcare Informatics, Premier Inc, Charlotte, NC) to estimate total US rFVIIa usage and the range of procedure codes associated with its use. Premier Healthcare Informatics samples 450 acute care facilities with approximately 18 million inpatient records to estimate national medication usage. Usage estimates for 2004 were annualized from data for the first 6 months. Additional information about this database can be found at <http://www.premierinc.com/all/prs/services/perspectiverx.jsp>.

For time intervals between last rFVIIa doses and first symptoms or signs of thromboembolic AEs, we estimated time to the closest hour when reports included sufficient detail. For reports that provided dates but not time of day, we assigned 24 hours to each day elapsed. We did not include reports without exact dates unless the reporter specified elapsed time. Occurrence during the rFVIIa infusion is denoted as 0 hours. All US and non-US AERS reports (postlicensure trial and spontaneous) with sufficient timing information were included.

Because our work reflects the FDA's ongoing public health safety surveillance for licensed biologic products, institutional review board approval was not needed.

RESULTS

Based on Premier Healthcare Informatics data, the estimated number of hospitalized patients treated with rFVIIa in the United States increased from 349 in 2000 (the first full year after licensure) to 4520 in 2004 (FIGURE 1). The array of different hospital discharge *International Classification of Diseases, Ninth Revision (ICD-9)*⁵ codes associated with rFVIIa use has also increased during this period (FIGURE 2).

We identified a total of 431 AE reports for rFVIIa from March 25, 1999, through December 31, 2004. Of these 431 reports, 168 reports, the main focus of our analysis, described 185 thromboembolic events. Of the 263 excluded reports, 22 fatality reports lacked details to support classification as thromboembolic or nonthromboembolic events and 241 reports described nonthromboembolic AEs. A total of 193 nonthromboembolic AEs (80%) had coding terms related to lack of the product's intended effect or to progression of an underlying disease. The remainder (n=48) of the nonthromboembolic AEs were reports of nausea, vomiting, rash, allergic reactions, various laboratory abnormalities, and/or pain. The nonthromboembolic event reports were not further analyzed.

Demographics

The median age of the patients with a thromboembolic event was 52 years (range, 1 month to 91 years); 65% of the patients were men. Fifty-nine (35%) of 168 thromboembolic event reports involved patients enrolled in postlicensure trials. Numbers of spontaneous thromboembolic reports increased annually from 1999 through 2004 (FIGURE 3). In contrast, the smaller but generally increasing numbers of trial reports declined in 2004. Reports from the United States accounted for 43% of spontaneous reports and 5% of trial reports.

Reasons for Use

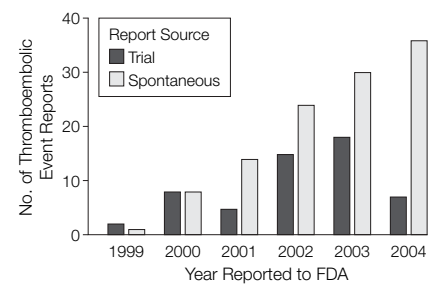
All of the 59 thromboembolic trial reports described unlabeled uses in patients with-

out hemophilia. A total of 92 (84%) of 109 spontaneous reports also identified unlabeled uses, including 16 patients with acquired hemophilia. Surgery (either bleeding or prophylaxis in cardiothoracic, liver transplantation/resection, and trauma procedures) was the most common indication among spontaneous and trial reports (TABLE 1). Of 22 spontaneous reports after prophylactic use of rFVIIa (Table 1), 7 patients had congenital hemophilia and 5 had acquired hemophilia.

Sites of Thromboembolic Events

The proportional distribution of reported thromboembolic event sites was largely similar among trial and spontaneous reports (TABLE 2). The 99 arterial events (54.1%) included 39 embolic/thrombotic cerebrovascular accidents (21.3%) and 34 acute myocardial infarctions (18.6%). The remaining 26 arterial thromboembolic events (14.2%) involved femoral, hepatic, pulmonary, renal, splenic, and iliac artery occlusion. There were 32 reports of pulmonary emboli (17.5%) and 42 reports of deep vein thrombosis and/or jugular, mesenteric, portal, renal, and retinal vein thromboses (22.9%). Nine of the 10 reports for device occlusion after rFVIIa administration were not trial related. The devices included extracorporeal membrane oxygenation lines, dialysis shunts/

Figure 3. Number of Thromboembolic Event Reports With Recombinant Human Coagulation Factor VIIa Reported to FDA by Source and Year



FDA indicates US Food and Drug Administration. Some reports had more than 1 thromboembolic event.

Table 1. Number of Thromboembolic Event Reports With Use of rFVIIa by Report Source and Reason for Use and Bleeding Status

	No. of Reports (%)	
	Trial (n = 59)	Spontaneous (n = 109)
Reason for use		
Surgery (bleeding or prophylaxis)	27 (46)	48 (44)
Intracranial bleeding	19 (32)	5 (4)
Bleeding, nonsurgical	8 (14)	26 (24)
Trauma, nonsurgical	5 (8)	9 (8)
Hemophilia	0	17 (16)
Unknown*	0	4 (4)
Bleeding status		
Active bleeding	35 (59)	80 (73)
Prophylaxis	24 (41)	22 (20)
Unknown*	0	7 (7)

Abbreviation: rFVIIa, recombinant human coagulation factor VIIa.

*Indicates no information about reason for use or whether patient was bleeding or not.

Table 2. Number of Thromboembolic Events Reported With Use of rFVIIa by Site and Report Source*

Site	No. of Reports (%)		
	Trial	Spontaneous	Total
Arterial	37 (20.2)	62 (33.9)	99 (54.1)
Non-ICH cerebrovascular accident	13 (7.1)	26 (14.2)	39 (21.3)
Acute myocardial infarction	12 (6.5)	22 (12.0)	34 (18.6)
Other arterial thromboembolism†	12 (6.5)	14 (7.6)	26 (14.2)
Venous	28 (15.3)	46 (25.1)	74 (40.4)
Venous other than pulmonary embolus‡	18 (9.8)	24 (13.1)	42 (22.9)
Pulmonary embolus	10 (5.5)	22 (12.0)	32 (17.5)
Device occluded§	1 (0.5)	9 (4.9)	10 (5.5)
Total	66 (36.1)	117 (63.9)	183 (100)

Abbreviations: ICH, intracerebral hemorrhage; rFVIIa, recombinant human coagulation factor VIIa.

*Excluding 2 spontaneous reports with unstated thromboembolism site.

†Includes femoral, hepatic, pulmonary, renal, splenic, and iliac artery occlusion.

‡Includes deep vein thrombosis and/or jugular, mesenteric, portal, renal, and retinal vein thromboses.

§Device includes extracorporeal membrane oxygenation lines, dialysis shunts/tubing, and endotracheal tubes.

tubing, and endotracheal tubes. Seventeen spontaneous reports for patients with hemophilia and inhibitors described 12 venous and 7 arterial thromboses, including 4 cerebrovascular accidents and 3 acute myocardial infarctions.

Approximately 90% of the reports included the diagnostic methods used to evaluate the AEs. These methods varied according to the type of thrombotic event suspected (eg, electrocardiogram and troponin, cerebral computed tomography/magnetic resonance imaging). Most other reports had diagnostic confirmation through subsequent events (eg, limb amputation after arterial thrombosis, vena cava umbrella after deep vein thrombosis, or coronary artery bypass graft surgery after acute myocardial infarction).

Mortality

Spontaneous reports account for most of the increase in reported deaths

among thromboembolism cases after 2001 (FIGURE 4). The probable cause of death was the thromboembolic event in 36 (72%) of 50 reported deaths, based on autopsy findings (n=9) or definitive clinical information, such as electrocardiogram, cardiac enzymes, or angiographic studies (n=27).

Temporal Association

There was sufficient information in 144 reports to estimate the interval from the last dose of rFVIIa to the first documented sign or symptom of the thromboembolic event (FIGURE 5). The median time period was approximately 24 hours. These intervals ranged from occurrence during the rFVIIa infusion to 1 month postinfusion. Seventy-three events (52%) occurred in the first 24 hours after the last dose, including 30 events within 2 hours.

Concomitant Products and Medical Conditions

Use of concomitant hemostatic agents was mentioned in 64 (38%) of 168 reports. The most commonly reported products were platelets (n=14 reports) and fresh-frozen plasma (n=14 reports). Other products included drugs, such as ϵ -aminocaproic acid (n=13), cryoprecipitate (n=7), and coagulation factors other than rFVIIa, including anti-inhibitor coagulant complex (n=8).

Most reports did not adequately document presence of underlying medical conditions. Only 17 reports described history of coronary atherosclerotic heart disease or stroke. Fourteen reports noted that the patient had cancer and 4 reports identified serious concomitant in-

fections. Ten reports specified the presence (n=4) or absence (n=6) of conditions associated with abnormal clotting; the remaining 158 reports contained no information. The 4 specific abnormalities were activated protein C resistance, lupus anticoagulant, paroxysmal nocturnal hemoglobinuria, and protein C or S deficiency.

Primary Reporters' Causality Assessment

Of the 168 reports, 102 (61%) included a causality assessment. A probable or possible causal relationship was provided in 81 reports and an unlikely causal relationship in the remaining 21 reports. Of the reports with an assessment, 94% were from health care professionals.

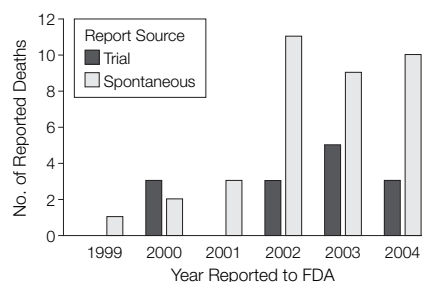
COMMENT

Our review of the FDA's AERS database for the initial 5 years after the US licensure of rFVIIa identified 185 thromboembolic events in 168 patients. Most reports of thromboembolic events followed use of rFVIIa for a variety of unlabeled indications in patients without hemophilia.

Recombinant FVIIa-induced thrombosis at locations other than the target bleeding site is biologically plausible. The rate of thrombin generation induced by rFVIIa in normal plasma is greater than in hemophilia A or hemophilia B plasma in vitro.⁶ High levels of rFVIIa in vitro accelerate thrombin generation in the apparent absence of tissue factor^{7,8} and the pharmacological effect of rFVIIa may not be limited to the surface of activated platelets at the bleeding site.⁹⁻¹¹ These findings are of uncertain clinical significance but suggest that rFVIIa might be more thrombogenic in patients without hemophilia and in patients with conditions predisposing to thrombosis, such as surgery, pregnancy, liver failure, congestive heart failure, or coronary artery disease, than in patients with hemophilia and inhibitor antibodies.

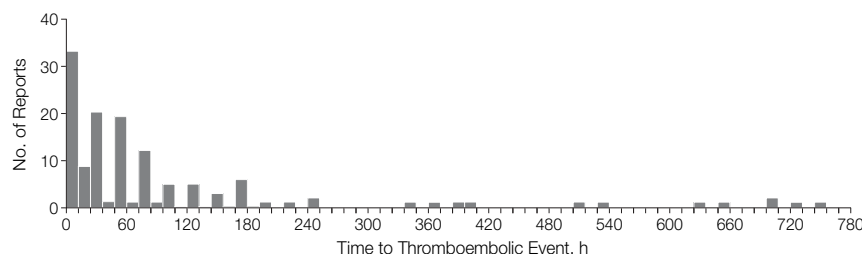
Inherent limitations of passive surveillance, such as incomplete case ascertainment and absence of exposure

Figure 4. Number of Reported Deaths Among Patients Administered Recombinant Human Coagulation Factor VIIa With a Thromboembolic Event by Year and Source



FDA indicates US Food and Drug Administration.

Figure 5. Number of Reports by Time From Last Recombinant Human Coagulation Factor VIIa Dose to Thromboembolic Event



data (total number of patients treated), preclude meaningful comparisons of reporting rates for thromboembolic events among different patient groups. Too few case reports had sufficient dosing information to evaluate potential dose-response relationships and many did not address other variables that might influence thromboembolic risk independent of rFVIIa, such as concomitant hemostatic medications, past history of thromboembolic events, or predisposing medical conditions. Among reports that did not identify concomitant hemostatic agents, we cannot distinguish between actual absence of use vs reporter omission of the information.

We observed a close temporal association between rFVIIa administration and many of the reported thromboembolic AEs in our series. This temporal relationship is consistent with the approximately 2-hour elimination half-life of rFVIIa,¹ especially because clinical evidence of thrombosis may not become immediately apparent. In addition, more than half of the reports included a causality assessment by the primary reporter, usually in the context of a clinical trial. More than 75% of these assessments concluded that a relationship between the thromboembolic event and rFVIIa was probable or possible. This apparent association, however, must be interpreted cautiously. Underlying conditions that can increase thrombotic risk are of particular importance. If obstetric hemorrhage, for example, prompts rFVIIa use and the patient subsequently develops a thromboembolic event, the apparent temporal association could reflect confounding by indication rather than an effect of rFVIIa.

The frequency of thromboembolic AEs cannot be determined from our spontaneous reporting system data. Primary reporting in this system is voluntary and most AEs are not reported. The precise extent of underreporting is unknown but likely is influenced by numerous factors, including time since a product's market introduction (Weber effect¹²), whether studies or registries are in progress, publicity, and the prod-

uct's perceived risk/benefit ratio. Recently published results of a randomized placebo-controlled rFVIIa trial for acute intracranial hemorrhage in patients without hemophilia demonstrated 3 times more thromboembolic AEs in recipients of rFVIIa than placebo, including 7 acute myocardial infarctions and 9 cerebrovascular accidents. No arterial thromboembolic AEs were found in the placebo group and thrombotic events increased with increasing rFVIIa dose.¹³ The primary end point in this phase 2 dose-ranging trial was not mortality or disability, but the combined rFVIIa groups had lower mortality without an increase in severe disability relative to the placebo group.

Our case series includes a variety of disease states in which the risks and benefits of rFVIIa may differ quantitatively, qualitatively, or both. The serious nature of the reported AEs, their biological plausibility, and the inherent limitations of passive surveillance underscore the need for randomized controlled trials with appropriate control groups and robust end points to elucidate the safety and efficacy of rFVIIa for each indication.

ADDENDUM

The FDA approved use of rFVIIa in 2005 for additional indications: surgical procedures in patients with hemophilia A or B and inhibitors and treatment of bleeding episodes in patients with factor VII deficiency.

Between January 1, 2005, and November 1, 2005, the FDA received another 168 AE reports for rFVIIa. Of these, 52 described patients experiencing 61 thromboembolic AEs. The characteristics of these reports do not differ materially from the 1999-2004 reports described and do not change our conclusions.

Reasons for Use

All but 6 of the 52 reports involved unlabeled uses of rFVIIa; the most common use was surgical bleeding, followed by nonsurgical hemorrhage. Six reports described prophylactic use, of which 3 were patients with

hemophilia or factor VII deficiency. Twelve reports were from trials; 40 were spontaneous, of which 38% were US reporters.

Sites of Thromboembolic Events

A total of 30 arterial events, 26 venous events, and 5 events involving devices were found. The procedure used to diagnose the thromboembolic event was included in 73% of the reports.

Mortality

The outcome was fatal in 17 (33%) of the 52 reports; of these 17 reports, death was attributed to the thromboembolic event in 7 reports (41%).

Temporal Association

Thromboembolic events occurring within the first 24 hours of last rFVIIa dose accounted for 50% of the reports with adequate information for estimation (n=44). One report of cerebrovascular accidents within 24 hours occurred in a patient who had received 36 000 µg of rFVIIa twice.

Concomitant Products and Medical Conditions

Other hemostatic medications were described in 25 reports, the most common being fresh-frozen plasma and platelets. Underlying medical conditions included 7 patients with cancer, 2 with sepsis, and 9 with a history of atherosclerotic heart disease or stroke.

Primary Reporters' Causality Assessment

A probable or possible relationship to rFVIIa was noted in 71% of reports with reporter causality assessment (n=24) and an unlikely relationship was found in 29% of the reports.

Author Contributions: Drs O'Connell and Wood had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: O'Connell, Wood, Braun.

Acquisition of data: O'Connell, Wood.

Analysis and interpretation of data: O'Connell, Wood, Wise, Lozier, Braun.

Drafting of the manuscript: O'Connell, Wood, Wise, Lozier.

Critical revision of the manuscript for important intellectual content: O'Connell, Wood, Wise, Lozier, Braun.

Statistical analysis: Wood.

Administrative, technical, or material support: O'Connell, Braun.

Study supervision: O'Connell, Wise, Braun.

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It is the function of creative men to perceive the relations between thoughts, or things, or forms of expression that may seem utterly different, and to be able to combine them into some new forms—the power to connect the seemingly unconnected.

—William Plomer (1903-1973)