Pharmacological therapy of vascular malformations of the gastrointestinal tract

Andrew Szilagyi MD FRCPC, Maged P Ghali MD FRCPC

Vascular malformation (AVM) in the gastrointestinal tract is an uncommon, but not rare, cause of bleeding and iron deficiency anemia, especially in an aging population. While endoscopic coagulative therapy is the method of choice for controlling bleeding, a substantial number of cases require additional therapy. Adjunctive or even primary pharmacotherapy may be indicated in recurrent bleeding. However, there is little evidence-based proof of efficacy for any agent. The bulk of support is derived from anecdotal reports or case series. The present review compares the outcome of AVM after no intervention, coagulative therapy or focus on pharmacological agents. Most of the literature encompasses two common AVMs, angiodyplasia and hereditary hemorrhagic telangiectasia. Similarly, the bulk of information evaluates two therapies, hormones (estrogen and progesterone) and the somatostatin analogue octreotide. Of these, the former is the only therapy evaluated in randomized trials, and the results are conflicting without clear guidelines. The latter therapy has been reported only as case reports and case series without prospective trials. In addition, other anecdotaly used medications are discussed.

Key Words: Gastrointestinal; Malformations; Pharmacological; Therapy; Vascular

La pharmacothérapie des malformations vasculaires du tube digestif

Les malformations vasculaires (MV) du tube digestif sont une cause peu courante, mais non rare, d’hémorragie et d’anémie ferreuse, surtout chez les personnes âgées. Même si la coagulation endoscopique est l’intervention privilégiée pour juguler les hémorragies, il est souvent nécessaire de recourir à un traitement complémentaire. La pharmacothérapie d’appui et même celle de base peuvent être indiquées dans les cas de récidive. Toutefois, l’on dispose de bien peu de données factuelles sur l’efficacité d’un agent en particulier, et celles qui existent proviennent, pour la plupart, de cas isolés ou de séries de cas. Le présent examen établit une comparaison entre l’absence d’intervention, la coagulothérapie et la pharmacothérapie pour le traitement des MV du tube digestif. La majeure partie de la documentation porte sur deux grands types de MV, soit l’angiodyplasie et l’angiomatose hémorragique familiale. Il en va de même pour les traitements : la plupart des articles en évaluent deux types, soit les hormones (oestrogènes, progestérone) et l’analogue de la somatostatine (octréotide). En ce qui concerne le premier, il est le seul agent à avoir fait l’objet d’évaluation dans des essais cliniques avec hasardisation, et il s’en dégage des résultats divergents, sans ligne directrice clairement définie. Quant au dernier, on n’en fait état que dans des exposés de cas ou des séries de cas, et non dans des essais prospectifs. Enfin, il sera question d’autres médicaments utilisés dans des cas isolés.
Szilagyi and Ghali

TABLE 1
Rebleeding rate following the last episode of bleeding in control groups of patients with gastrointestinal vascular malformations

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Patients (n)</th>
<th>Average follow-up (months)</th>
<th>No further bleeding, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richter et al (20)</td>
<td>36</td>
<td>22</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Lewis et al (21)</td>
<td>34</td>
<td>13.4</td>
<td>15 (44)</td>
</tr>
<tr>
<td>Junquera et al (22)</td>
<td>35</td>
<td>12</td>
<td>19 (54)*</td>
</tr>
</tbody>
</table>

*Increased risk of rebleeding with greater transfusion requirements before study entry

PATHOGENESIS

Pathogenesis of AD was reported by Boley et al (11) to be a natural sequence of vascular ‘degeneration’ with aging. In their original description, chronic, intermittent obstruction of perforating mucosal vessels in elderly subjects ultimately led to progressive vascular dilation and new perforating vessel formation. An initial explanation placed areas like the cecum into high risk for AD development based on the law of Laplace. Because the cecum has the widest diameter, the highest wall tensions and subsequent occlusive processes could occur in this location (11). This hypothesis was less able to explain anomalies at other locations and the reason for bleeding.

A more recent development is the understanding that chronic, low-grade, intermittent obstruction of vessels leads to local hypoxia. This, in turn, leads to the induction of a number of neovascular growth factors. This then helps to propagate new abnormal vessel formation (12,13).

Early explanations for continued bleeding included the development of microtrauma due to elements in stool and increased intravascular processes due to clinical conditions like congestive heart failure and portal hypertension (11,14). Subsequently Warkentin et al (15) proposed a possible explanation as to why there may be a higher risk of AD bleeds in valvular disease (especially aortic stenosis, Heyde’s syndrome). This group hypothesized that the high shear forces across the stenotic valves lead to loss of large molecular weight multimers of von Willebrand factor. This loss predisposes exposed protein to proteolysis and results in poor thrombus formation. In the ADs of the GI tract, abnormal shear forces help to localize and focus the abnormality, resulting in prolonged bleeding. Warkentin et al (15) hypothesized that this acquired von Willebrand syndrome IIA may occur in a number of cardiovascular conditions. Subsequently, an inverse association between the severity of aortic stenosis and levels of von Willebrand factor was described by an independent group (16). These levels diminished and bleeding improved in patients who underwent valvular surgery.

In HHT, an autosomal dominant disorder that occurs in four to five people of every 100,000 in the population, nose bleeds occur in over 90%, and the lung, liver and brain can be involved as well. Generally, GI bleeding occurs in the fourth to fifth decade from predominantly proximal lesions (4).

At least two well-defined genetic abnormalities, both affecting tumour growth factor-beta receptors, lead to vascular fragility (4). These vessels show increased elements of fibrinolysis under examination (17). However, elevated vascular endothelial growth factor was also described and believed to contribute to bleeding (18).

TABLE 2
Rebleeding rate following the last episode of bleeding in patients treated with various coagulative methods for gastrointestinal vascular malformations

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Patients (n)</th>
<th>Site</th>
<th>Patients requiring more interventions, n (%)</th>
<th>Median follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard et al (23)</td>
<td>23</td>
<td>Colon</td>
<td>11 (50)</td>
<td>17</td>
</tr>
<tr>
<td>Bown et al (24)</td>
<td>18</td>
<td>Stomach</td>
<td>6 (33.3)</td>
<td>60</td>
</tr>
<tr>
<td>Pottamiano et al (25)</td>
<td>8</td>
<td>Stomach</td>
<td>3 (37.5)</td>
<td>19.5</td>
</tr>
<tr>
<td>Rutgeerts et al (26)</td>
<td>59</td>
<td>Diffuse</td>
<td>17 (29.8)</td>
<td>11.5</td>
</tr>
<tr>
<td>Cello and</td>
<td>43</td>
<td>Diffuse</td>
<td>22 (51)*</td>
<td>12</td>
</tr>
<tr>
<td>Grendell (27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gostout et al (28)</td>
<td>93</td>
<td>Diffuse</td>
<td>12 (12.9)</td>
<td>12</td>
</tr>
<tr>
<td>Roberts et al (29)</td>
<td>13</td>
<td>Colon</td>
<td>3 (23.1)</td>
<td>24</td>
</tr>
<tr>
<td>Lanthier et al (30)</td>
<td>26</td>
<td>Colon</td>
<td>5 (19)</td>
<td>29</td>
</tr>
<tr>
<td>Mathus-Vliegen (31)</td>
<td>107</td>
<td>Diffuse</td>
<td>36 (34)</td>
<td>18</td>
</tr>
<tr>
<td>Naveau et al (32)</td>
<td>47</td>
<td>Diffuse</td>
<td>15 (32)</td>
<td>19</td>
</tr>
<tr>
<td>Sargeant et al (33)</td>
<td>41</td>
<td>Stomach</td>
<td>12 (29)</td>
<td>44</td>
</tr>
<tr>
<td>Gupta et al (34)</td>
<td>16</td>
<td>Colon</td>
<td>5 (31.2)</td>
<td>13.5</td>
</tr>
<tr>
<td>Total</td>
<td>492</td>
<td></td>
<td>142 (28.9)*</td>
<td>23.3</td>
</tr>
</tbody>
</table>

*Rebleeding rate was higher from an upper gastrointestinal tract source, associated coronary artery disease and the number of transfusions required before coagulative therapy; 1Rebleeding

Other less common AVMs such as hemangiomas (true vascular tumours), gastric vascular ectasia and blue rubber bleb nevus syndrome have other potential mechanisms of formation (4,19). However, the role of vascular growth factors have not been adequately studied in these other conditions.

The role of intermittent vascular obstruction with subsequent induction of endothelial growth factors, as well as the development of poorly functional von Willebrand factor and subsequent poor clot formation, offer potential targets of medical therapy.

NATURAL AND TREATED HISTORY

It is important to consider the natural history of these lesions in terms of incidental findings, spontaneous rebleeding or after therapeutic intervention. The finding of AVMs of the colon (mainly AD) in asymptomatic, nonbleeding, nonanemic patients does not usually prompt initiation of therapy. An early study from the Mayo Clinic (20) reported 15 such patients for 23 months and found that none bled during the period of observation. A much larger study by Foutch et al (2) reported a prevalence of 0.83% (eight of 964, all over 50 years of age) at screening colonoscopy. These eight patients were followed for 36 months and none bled.

The risk of rebleeding after an initial episode can be gleaned from the control population of three published studies (Table 1) (20-22). In these three publications, 105 patients were treated with supportive therapy only (transfusions and hydration). During an average follow-up period of 15.8 months, 50.9% of the patients failed to rebleed. Junquera et al (22) also noted that the risk of rebleeding was amplified with an increasing transfusion requirement before current bleeding. In contradistinction, a summary of reports of various coagulative therapy for both upper and lower GI bleeds resulting mainly from AD is shown in Table 2 (23-34). Of 492 patients with
TABLE 3
Pharmacological agents used for treatment of vascular malformations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Predominant diagnosis</th>
<th>Route and dose</th>
<th>Putative mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen (E)</td>
<td>AD/HHT</td>
<td>0.035 mg–0.05 mg po</td>
<td>Vascular stability, improved coagulation, decreased mesenteric blood flow</td>
<td>41-43,55</td>
</tr>
<tr>
<td>E + progesterone (P)</td>
<td>AD/HHT</td>
<td>0.01 mg–0.1 mg po (E), 1 mg–2 mg po (P)</td>
<td>Vascular stability, improved coagulation, decreased mesenteric blood flow</td>
<td>21,22,44-57</td>
</tr>
<tr>
<td>Octreotide</td>
<td>AD/HHT, BRBNS</td>
<td>100 mg–500 mg sc bid, 10 mg–30 mg im</td>
<td>Multiple effects</td>
<td>53,54</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>WS</td>
<td>po</td>
<td>Increased vascular integrity</td>
<td>79,80</td>
</tr>
<tr>
<td>Prednisolone + cyclophosphamide</td>
<td>WS po</td>
<td>Increased vascular integrity</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Interferon</td>
<td>Hemangiommas</td>
<td>sc</td>
<td>Inhibits angiogenesis</td>
<td>82</td>
</tr>
<tr>
<td>Danazol</td>
<td>HHT</td>
<td>200 mg po tid</td>
<td>Weak androgen, direct vascular stability</td>
<td>83</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>HHT</td>
<td>1 g po qid</td>
<td>Inhibits fibrinolysis</td>
<td>84,85</td>
</tr>
<tr>
<td>Aminocaproic acid</td>
<td>HHT</td>
<td>2 g po daily</td>
<td>Inhibits fibrinolytic system</td>
<td>86,87</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>HHT</td>
<td>IV</td>
<td>Stabilizes vessel wall, increased platelet adhesion</td>
<td>88</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>AD/IVIA</td>
<td></td>
<td>Decreased splanchnic circulation</td>
<td>89</td>
</tr>
<tr>
<td>Diamino-8-D-arginine</td>
<td>AD + VWD</td>
<td>IN spray, 300 µg</td>
<td>Increased vascular stability</td>
<td>90,91</td>
</tr>
<tr>
<td>vasopressin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>AD, HHT</td>
<td>100 mg–300 mg qid, 400 mg po daily</td>
<td>Antiangiogenesis</td>
<td>92-94</td>
</tr>
</tbody>
</table>

AD Angiodysplasia; bid Two times per day; BRBNS Blue rubber bleb nevus syndrome; HHT Hereditary hemorrhagic telangiectasia; IA Intra-arterial; im Intramuscular; IN Intranasal; IV Intravenous; po Orally; qid Four times per day; sc Subcutaneous; tid Three times per day; VWD von Willebrand disease; WS Watermelon stomach

In the small bowel, may be more difficult to treat. Recurrent bleeding is more likely if prior transfusion requirements are extensive, and if lesions are multiple and perhaps located proximally in the small bowel. Therefore, pharmacological therapy may be considered as adjunctive measures in patients in whom the above conditions prevail, in whom bleeding recurs despite repeated coagulative therapy and in whom surgery is not feasible (eg, elderly patients with multiple comorbid conditions).

**PHARMACOLOGICAL AGENTS USED IN THE TREATMENT OF AVMs**

Table 3 outlines published pharmacological agents for GI bleeding from AVM. With few exceptions, treatments are collections of anecdotal reports without the benefit of modern, controlled trials.

The most extensively studied pharmacological agents are the hormones estrogen and progesterone. Their use was originally based on the observation that epistaxis due to HHT improved with pregnancy and worsened in postmenopausal women (41). Although a large case series successfully using estrogen for epistaxis was published by Harrison (42), a randomized controlled trial (including only two cases of GI bleeding) failed to show benefit (43). Subsequently, combination estrogen and progesterone therapy was used for a variety of AVMs, including AD and HHT, affecting the gut. The exact mechanism of how hormones improve bleeding from such vessels has not been elucidated. However, a number of hypotheses have been proposed to explain beneficial effects (42). These include: stabilization of fragile vessels through increased keratinization of surrounding squamous epithelium; reduction of leaking from fragile capillaries; improvement of possible coagulation abnormalities; shortening of bleeding time; improved...
The rate of bleeding between the two groups (21). The most recent one year after follow-up, there was no significant difference in the rate of bleeding before entry into the study. However, a little over half of the patients treated with only high-dose estrogen stopped bleeding. Treated patients and controls were well-matched for site of bleeding. The majority (38 patients) were treated with a combination of hormones and some (five patients) were treated with estrogen alone.

In the study by Lewis et al (21), small bowel telangiectasia in patients with platelet disorders (eg, in association with Bernard-Soulier syndrome) (51,52). These publications included 22 case reports with either arrest of bleeding or an important reduction of transfusion requirements and an increase in hemoglobin for the duration of follow-up. Included is a case series of cirrhotic patients treated with hormonal therapy for watermelon stomach. Four of six patients stopped bleeding, one improved and one failed (44).

In addition to published cases and case series, there are five controlled trials on the use of hormonal therapy (21,22,55-57). However, the first crossover study published by Van Cutsem et al (56) was somewhat extended in another publication (57) reducing the comparisons among four different studies (Table 4). It should be noted that these studies are heterogeneous in type of patients included, method of study (double-blind, crossover; unblinded, randomized controlled; and double-blind or randomized, controlled), associated with or without additional therapy.

Two crossover trials both showed a significant decrease in transfusion requirements. Both included a mixed group of patients. In the study by Van Cutsem et al (57), 46% of subjects had HHT and the rest had AD. A very significant drop in transfusion requirements was noted. In the report of Barkin and Ross (55), 58% of proximal ADs were found and cataract at endoscopy, while in the remainder, no obvious bleeding site was found. The majority (38 patients) were treated with a combination of hormones and some (five patients) were treated with only high-dose estrogen. Bleeding stopped in patients treated with combination hormones but not with estrogen alone.

Very different results were reported in the two prospective controlled trials. In the study by Lewis et al (21), small bowel ADs were identified, and patients were treated with relatively high-dose estrogen and progesterone if they agreed to participate. Treated patients and controls were well-matched for site of bleeding before entry into the study. However, a little over one year after follow-up, there was no significant difference in rate of bleeding between the two groups (21). The most recent study by Junquera et al (22) is the only controlled, randomized double-blind trial of hormonal combination therapy and it also failed to find a therapeutic benefit over placebo. While the groups appeared well matched, there were more acute bleeders in the placebo group, and such patients may have a reduced risk of rebleeding during the period of follow-up. An additional criticism of the study was that the dose of estrogen used was one of the lowest reported and might also have influenced the lack of therapeutic benefit (58). It is difficult to summarize the outcome of these four publications because of the heterogeneity of the reports. It is known whether different types of vascular lesions respond differently. It is unclear whether prior coagulative treatment followed by pharmacological therapy improved outcome. Similarly, dose effects are not clearly delineated and might have impacted on outcome, as suggested by Van Cutsem et al (57). Finally, it may be important to compare patients with similar bleeding rates and order of bleeding episodes to take into consideration variable natural historical outcome. There are only suggested guidelines as to how long therapy should continue (8). In the case of initial failure, an increase in dose was recommended, and following additional failure, an alternate agent was suggested. In the case of success, a six-month period of therapy was suggested, after which holding hormonal treatment could be tried. If rebleeding occurred, the cycle could be repeated.

At this time, therefore, there are no clear guidelines on the effectiveness of estrogen and progesterone. Furthermore, there are a number of potential restrictions on the use of these hormones. For example, history of gynecological cancer, previous thromboembolic disease and, perhaps, chronic liver disease prohibit the use of this therapy (42). In addition, there are several side effects that may limit use. Some of these are mild: nausea, breast tenderness and enlargement, weight gain, loss of libido, intermenstrual or postmenopausal bleeding and, possibly, increased risk of endometrial cancer (42). Most serious effects relate to thromboembolic events, myocardial infarction and congestive heart failure. Interestingly, the distribution of these effects was not found to be in a relative risk- and limited in the crossover studies (55,57). However, the controlled trials reported a frequency of these effects more than fourfold over the crossover trials, and as well, side effects included some more serious outcomes (deep vein thrombophlebitis or ischemic stroke) (21,22).

The second most frequently reported pharmacological agent is that of the somatostatin analogue octreotide. There are potential ways in which this drug could impact on cessation and pre-

### TABLE 4
Summary of studies using hormonal therapy for gastrointestinal vascular malformations

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Type of study</th>
<th>Control (n)</th>
<th>Treated (n)</th>
<th>Transfusions before</th>
<th>Transfusions after</th>
<th>P</th>
<th>Follow-up before (months)</th>
<th>Follow-up after (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Cutsem et al (57)</td>
<td>DB, crossover</td>
<td>13</td>
<td>13</td>
<td>1.9/month*</td>
<td>0.18/month</td>
<td>0.002</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Lewis et al (21)</td>
<td>Controlled</td>
<td>34</td>
<td>30</td>
<td>1.8/month*</td>
<td>1.6/month</td>
<td>NS</td>
<td>13.4*</td>
<td>15.6*</td>
</tr>
<tr>
<td>Barkin and Ross (55)</td>
<td>Crossover, controlled</td>
<td>43</td>
<td>43</td>
<td>1.1/month</td>
<td>0/month</td>
<td>&lt;0.05</td>
<td>44.6 (n=38)</td>
<td></td>
</tr>
<tr>
<td>Junquera et al (22)</td>
<td>DB, RCT</td>
<td>35</td>
<td>33</td>
<td>1.7±1.5/12 months*</td>
<td>1.8±1.2/12 months</td>
<td>NS</td>
<td>20</td>
<td>(29.5) (n=5)*</td>
</tr>
</tbody>
</table>

*Control; †Treated; ‡All patients treated with only estrogen failed. DB Double-blind; NS Not significant; RCT Randomized controlled trial

Results of treatment with estrogen alone in doses ranging from 0.035 mg to 0.05 mg, or estrogen 0.01 mg to 0.1 mg and progesterone 1 mg to 5 mg have been published with reasonable success on anecdotal basis. Lesions include watermelon stomach (44-47), AD (48-52), HHT (41,53,54) and other telangiectasia in patients with platelet disorders (eg, in association with Bernard-Soulier syndrome) (51,52). These publications included 22 case reports with either arrest of bleeding or an important reduction of transfusion requirements and an increase in hemoglobin for the duration of follow-up. Included is a case series of cirrhotic patients treated with hormonal therapy for watermelon stomach. Four of six patients stopped bleeding, one improved and one failed (44).

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The second most frequently reported pharmacological agent is that of the somatostatin analogue octreotide. There are potential ways in which this drug could impact on cessation and pre-
vent of bleeding. These mechanisms include inhibition of peptic, gastric and acid secretion (59), improved platelet aggregation (60), decreased duodenal and splanchic blood flow (61), increased vascular resistance (62) and inhibition of angiogenesis (63).

Unlike published trials on hormones, most evidence on the benefits of octreotide is based on anecdotal case reports or case series only. Nevertheless, two publications on outcome analysis for the use of enteroscopy (64) or wireless capsule endoscopy (7) list octreotide as the primary form of medical therapy for AVMs. To date, there are 18 published cases of the use of octreotide in 13 adults (65-73) and five children (66,74,75). The mean follow-up in these reports was 20.1 months (range 0.1 to 64 months). In adults, the doses of octreotide ranged from 100 µg subcutaneously two times per day to 500 µg subcutaneously two times per day. In three of these adult patients, long-acting release intramuscular octreotide was used with a median dose of 20 mg per 28 days (70). In children, the dose ranged from 4 µg/kg to 8 µg/kg (75).

Seven of 18 (38.9%) of these children drastically reduced or arrested bleeding in three patients within four weeks and in HHT, in which danazol 20 mg orally three times per day (84). Subsequently, interferon (82,83).

However, it failed in two cases that subsequently responded to decreased bleeding in one case of hemangioma in children. transfection requirements (80,81). Similarly, prednisone three times per day in another instance resulted in improved that prednisone 5 mg/day to 15 mg/day in one case and 10 mg three times per day in another instance resulted in improved transfusion requirements (80,81). Similarly, prednisone decreased bleeding in one case of hemangioma in children. However, it failed in two cases that subsequently responded to interferon (82,83).

Because estrogen and progesterone were associated with numerous side effects, the weak androgen danaol was proposed as treatment for epistaxis in HHT (84). Subsequently, Korzenik et al (85) reported five cases of GI-related bleeding in HHT, in which danaol 20 mg orally three times per day arrested bleeding in three patients within four weeks and

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Concomitant promoter</th>
<th>n</th>
<th>Type of therapy</th>
<th>Follow-up (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Junquera et al (22)</td>
<td>Anticoagulant</td>
<td>1</td>
<td>Hormonal</td>
<td>12</td>
<td>Failed</td>
</tr>
<tr>
<td>Nordquist and Wallach (71)</td>
<td>Anticoagulant</td>
<td>1</td>
<td>IV octreotide</td>
<td>0.17</td>
<td>Succeeded</td>
</tr>
<tr>
<td>Blich et al (73)</td>
<td>Anticoagulant</td>
<td>1</td>
<td>Octreotide</td>
<td>28</td>
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<td>Junquera et al (22)</td>
<td>Acetylsalicylic acid</td>
<td>3</td>
<td>Hormonal</td>
<td>12</td>
<td>Failed</td>
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<tr>
<td>Nonsteroidal anti-inflammatory drug</td>
<td>Unspecified coagulopathy</td>
<td>1</td>
<td>Hormonal</td>
<td>12</td>
<td>Failed</td>
</tr>
<tr>
<td>Bowers et al (69)</td>
<td>Von Willebrand syndrome</td>
<td>2</td>
<td>Octreotide</td>
<td>11.5</td>
<td>Succeeded</td>
</tr>
<tr>
<td>Rahmani et al (92)</td>
<td>Von Willebrand syndrome</td>
<td>1</td>
<td>DDAVP</td>
<td>Unclear</td>
<td>Failed</td>
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<tr>
<td>Ahnmoed et al (93)</td>
<td>Von Willebrand syndrome</td>
<td>1</td>
<td>DDAVP</td>
<td>Unclear</td>
<td>Partial</td>
</tr>
<tr>
<td>Meijer et al (97)</td>
<td>Von Willebrand syndrome</td>
<td>1</td>
<td>Factor Vila</td>
<td>Unclear</td>
<td>Succeeded</td>
</tr>
<tr>
<td>Zanon et al (98)</td>
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<td>1</td>
<td>Factor VIII</td>
<td>12</td>
<td>Succeeded</td>
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<tr>
<td>Nardone et al (77)</td>
<td>Glanzmann thrombasthenia</td>
<td>1</td>
<td>Octreotide</td>
<td>6</td>
<td>Succeeded</td>
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<tr>
<td>Coppola et al (72)</td>
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<td>1</td>
<td>Octreotide</td>
<td>9</td>
<td>Unclear</td>
</tr>
<tr>
<td>Belucci et al (51)</td>
<td>Bernard-Soulier syndrome</td>
<td>1</td>
<td>Hormonal</td>
<td>22</td>
<td>Partial</td>
</tr>
<tr>
<td>Yaukel et al (52)</td>
<td>Bernard-Soulier syndrome</td>
<td>1</td>
<td>Hormonal</td>
<td>60</td>
<td>Failed</td>
</tr>
</tbody>
</table>

DDAVP Diamino-8-D-arginine vasopressin; IV Intravenous
the effects were maintained for 6.7 months to 30 months. The treatment failed in one patient and was of equivocal benefit in one more patient.

A number of cases are reported using the antifibronolytic agent tranexamic acid (TA) (86,87) and epsilon amino caproic acid (EACA) (88,89). While most of the 10 patients described suffered from epistaxis and HHT, at least three treated with EACA also had GI bleeding. The dose of TA was 4 g/day to 4.5 g/day in divided doses and the dose of EACA was 2 g/day to 3 g/day in divided doses. Bleeding decreased by 50% with TA and five of seven patients treated with EACA improved, with stoppage of bleeding for up to 10 to 34 months. Expected side effects of nausea, cramps, diarrhea, hypotension, dizziness, renal dysfunction or thrombosis did not occur.

In a patient with HHT, acute bleeding from GI and epistaxis, intravenous desmopressin at a dose of 0.4 µg/kg bolus over 30 min was found to decrease bleeding (90). This derivative of vasopressin is thought to increase platelet adhesion and release high molecular weight multimers of VWF from the endothelium (91-93).

The most recent addition to the list of pharmacological agents reported to be useful for bleeding AD is thalidomide (94-96). This drug, which was banned in the 1960s for inducing birth defects in pregnant mothers, made a comeback in the GI literature as an agent for Crohn’s disease. In high doses (400 mg/day), it has antitumour necrosis factor effects, while in lower doses (100 mg/day to 200 mg/day), it also has antiangiogenic effects. Five cases were published using this drug, one of HHT (97) and four of AD with poorly controlled GI bleeding (95,97). Patients improved in as little as two weeks, and the effect was sustained for a mean of 33 months (range 22 to 49 months). The main side effects were fatigue and transient peripheral neuropathy (especially at higher doses) (95,96).

A particularly difficult group to treat are patients with AVMs and associated coagulopathies, or obligate need for concomitant use of either anticoagulants or antiplatelet aggregative therapy. There are 22 such patients reported to be treated with a variety of medical therapies in various publications, with a mean follow-up of 16.4 months (range 0.17 to 60 months). Twelve patients were treated with a combination of estrogen and progesterone (22,51,52). Ten patients were from a single trial (22). However, partial success was achieved in only one patient (51). Octreotide was used in six patients and was reported to be successful in five of those patients (69,71-73,77). The only other therapy that met with success was the infusion factor VIIa (97) or factor VIII (98) in two patients with AD associated with von Willebrand disease. Due to the anecdotal nature of these reports, it is not possible to make any clear conclusions about the use of pharmacological therapy in these complex cases.

In summary, pharmacological management of AVM is a difficult undertaking and generally should be relegated to adjunctive use. There are few uniform guidelines and studies on which to base rational treatment. The best studied agents, estrogen and progesterone, have not been found to be uniformly successful and are controversial. Equally important is that hormones are associated with some significant side effects. While this is not the case for octreotide, reports are anecdotal and the drug has not benefitted from controlled trials. Other agents have even less basis for use, relying on a few anecdotal reports. More careful evaluation of pharmacological products is needed in this area as the population ages.

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