

Pharmacological therapy of vascular malformations of the gastrointestinal tract

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A Szilagyi, MP Ghali. Pharmacological therapy of vascular malformations of the gastrointestinal tract. *Can J Gastroenterol* 2006;20(3):171-178.

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, angiodysplasia 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 anecdotally used medications are discussed.

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

Vascular malformation (AVM) of the gastrointestinal (GI) tract represents an uncommon, but not rare, cause of GI bleeding (1,2). While 5% of upper GI hemorrhage may be related to such lesions, up to 30%, especially in elderly patients, may be related to AVMs and are the most frequent cause of obscure GI bleeds (3-5). Recent reports using push enteroscopy (6) or wireless capsule endoscopy (7) find angiodysplasia (AD) to be the most common AVM in the small bowel (45% and 29%, respectively).

While there is some discussion (4) of the classification of AVM from a clinical perspective, AD and, to a lesser extent, hereditary hemorrhagic telangiectasia (HHT) are the most common findings.

Presentation is usually episodic – less often with massive bleeding or more commonly with iron deficiency anemia together with occult blood-positive stools. Management has

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 ferriprive, 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'appoint et même celle de base peuvent être indiquées dans les cas de récurrence. 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'angiodysplasie et l'angiomasose 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 pas dans des essais prospectifs. Enfin, il sera question d'autres médicaments utilisés dans des cas isolés.

become better defined with the use of endoscopic coagulative therapy. However, complex cases still plague clinicians. In many patients, control of hemorrhage is made more difficult by the multiple sites involved, or by poorly accessible regions like the ileum or the proximal jejunum.

The present review focuses on available reports (in English) of pharmacological therapy for AD, HHT and several other GI AVMs. Pharmacological agents are discussed in the context of plausible biological effects. By necessity, the pathogenesis of the two most common delineated AVMs (AD and HHT) are the basis of discussion for potential mechanisms of effect. Few recent publications on this topic are available (8-10). Comparisons of outcomes among different therapeutic modalities are only for descriptive purposes and are not meant to be interpreted with statistical analyses.

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Received for publication July 21, 2005. Accepted September 19, 2005

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

Author (reference)	Patients (n)	Average follow-up (months)	No further bleeding, n (%)
Richter et al (20)	36	22	19 (54)
Lewis et al (21)	34	13.4	15 (44)
Junquera et al (22)	35	12	19 (54)*

*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, nosebleeds 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

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

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

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

Drug	Predominant diagnosis	Route and dose	Putative mechanism	References
Estrogen (E)	AD/HHT	0.035 mg–0.05 mg po	Vascular stability, improved coagulation, decreased mesenteric blood flow	41-43,55
E + progesterone (P)	AD/HHT	0.01 mg–0.1 mg po (E), 1 mg–2 mg po (P)	Vascular stability, improved coagulation, decreased mesenteric blood flow	21,22,44-57 53,54
Octreotide	AD/HHT, BRBNS	100 mg–500 mg sc bid, 10 mg–30 mg im	Multiple effects	64-76
Corticosteroids	WS	po	Increased vascular integrity	79,80
Prednisolone + cyclophosphamide	WS	po	Increased vascular integrity	81
Interferon	Hemangiomas	sc	Inhibits angiogenesis	82
Danazol	HHT	200 mg po tid	Weak androgen, direct vascular stability	83
Tranexamic acid	HHT	1 g po qid	Inhibits fibrinolysis	84,85
Aminocaproic acid	HHT	2 g po daily	Inhibits fibrinolytic system	86,87
Desmopressin	HHT	IV	Stabilizes vessel wall, increased platelet adhesion	88
Vasopressin	AD	IV/IA	Decreased splanchnic circulation	89
Diamino-8-D-arginine vasopressin	AD + VWD	IN spray, 300 µg	Increased vascular stability	90,91
Thalidomide	AD, HHT	100 mg–300 mg qid 400 mg po daily	Antiangiogenesis	92-94

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

different sites of bleeding, only 142 rebled in an average follow-up period of 23.3 months. Cello and Grendell (27) noted, as did Junquera et al, that more transfusions before current bleeding increased risk. As well, proximal lesions were more difficult to control.

In view of success achieved with endoscopic therapy, the primary role of surgery has diminished (35). Interestingly, however, an earlier comparison of outcomes among patients treated surgically, endoscopically or with nonpharmacological supportive therapy showed no significant differences in outcomes among the three modalities of treatment. Therapy with surgery, however, was 2.5 times less likely to lead to rebleeding in a 60-month follow-up period (20).

Outcomes of surgery for GI AVMs may partly depend on selecting candidates with favourable characteristics. For example, solitary acquired or congenital bleeding lesions in otherwise relatively well patients are better candidates than patients with multiple sites of potential bleeding with comorbid conditions (36). Indeed, in studies of nonselected patients with occult or obscure causes of GI bleeding, resection of AVMs led to rebleeding rates of 9.9% to 39%. The range of follow-up was 19 to 32 months (37-39). In one of these reports, the overall death rate was prohibitive at 7.5% (38).

There is little in the literature on outcomes of different pharmacological agents used compared with supportive therapy alone. A retrospective case series (40) compared various pharmacological agents in 40 HHT patients with supportive treatment alone and showed no significant advantage of the former over a 12-month follow-up period.

In summary, incidentally found vascular lesions (eg, at screening colonoscopy) do not need therapy. The best therapy is likely endoscopic if the lesions are few and easily reachable with instruments. However, multiple lesions, especially

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

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

Author (reference)	Type of study	Control (n)	Treated (n)	Transfusions before	Transfusions after	P	Follow-up before (months)	Follow-up after (months)
Van Cutsem et al (57)	DB, crossover	13	13	1.94/month	0.18/month	0.002	12 to 36	6
Lewis et al (21)	Controlled	34	30	1.8/month* 2.2/month†	1.6/month 1.5/month	NS		13.4* 15.6†
Barkin and Ross (55)	Crossover, controlled	43	43	1.1/month	0/month	<0.05		44.6 (n=38) (29.5) (n=5)‡
Junquera et al (22)	DB, RCT	35	33		1.76±1.5/12 months* 1.8±2.1/12 months†	NS		20 (12 to 36)

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

vasoconstrictive effect of vasopressin and noradrenaline (44); possible inhibition of angiogenesis; and reduction of mesenteric blood flow through increased stasis.

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).

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 cauterized 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 unknown 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 reported to be relatively mild 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 5
Published cases with gastrointestinal vascular malformations and concomitant therapy which can promote bleeding, coagulopathy or platelet disorders

Author (reference)	Concomitant promoter	n	Type of therapy	Follow-up (months)	Outcome
Junquera et al (22)	Anticoagulant	1	Hormonal	12	Failed
Nordquist and Wallach (71)	Anticoagulant	1	IV octreotide	0.17	Succeeded
Blich et al (73)	Anticoagulant	1	Octreotide	28	Succeeded
Junquera et al (22)	Acetylsalicylic acid	3	Hormonal	12	Failed
	Nonsteroidal anti-inflammatory drug	5	Hormonal	12	Failed
	Unspecified coagulopathy	1	Hormonal	12	Failed
Bowers et al (69)	Von Willebrand syndrome	2	Octreotide	11.5	Succeeded
Rahmani et al (92)	Von Willebrand syndrome	1	DDAVP	Unclear	Failed
Alhumood et al (93)	Von Willebrand syndrome	1	DDAVP	Unclear	Partial
Meijer et al (97)	Von Willebrand syndrome	1	Factor VIIa	Unclear	Succeeded
Zanon et al (98)	Von Willebrand syndrome	1	Factor VIII	12	Succeeded
Nardone et al (77)	Glanzmann thrombasthenia	1	Octreotide	6	Succeeded
Coppola et al (72)	Glanzmann thrombasthenia	1	Octreotide	9	Unclear
Belucci et al (51)	Bernard-Soulier syndrome	1	Hormonal	22	Partial
Yuksel et al (52)	Bernard-Soulier syndrome	1	Hormonal	60	Failed

DDAVP Diamino-8-D-arginine vasopressin; IV Intravenous

vention of bleeding. These mechanisms include inhibition of pepsin, gastrin and acid secretion (59), improved platelet aggregation (60), decreased duodenal and splanchnic 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 range 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 stopped transfusion requirements after treatment. A further nine of 18 children (50%) were able to reduce transfusion requirements noticeably; in one of 18 children (5.6%), the effect was equivocal (72); and in one of 18 children (5.6%), the treatment completely failed (68).

Two larger case series have been published. Pennazio et al (76) initially published an abstract on outcome of therapy, but little detail other than a claim of improvement could be gleaned. Two subsequent full paper publications by the same group (7,64) alluded to above do not make clear whether the reported patients were the same or different from those in the abstract. In any event, not enough clinical detail is provided in the publications to assess outcome comparison with other reports. The only other published series on the topic was provided by Nardone et al (77). In this series, seven patients had single and seven patients had multiple upper and lower GI AVMs; three patients had watermelon stomach. The outcome after a mean follow-up of 38.8 months (range 12 to 84 months)

showed that 10 of 17 patients (58.8%) completely stopped transfusion, four of seven patients (23.5%) decreased transfusion requirements, and in three of 17 patients (17.6%), there was no perceptible effect. In this study, 11 of 17 patients (65%) received previous endoscopic coagulative or angiographic therapy as well.

Side effects of octreotide were generally mild. These included early abdominal pain, diarrhea, weakness, taste perversion, skin rash, difficult-to-control glucose in diabetics and pain at intramuscular injection sites. The more serious side effects, such as development of gallstones, hypothyroidism, kidney stones, pancreatic enzyme deficiency (59,61,62) or the rare cardiovascular bradycardia and negative inotropic effects (78), were not seen. Regarding the latter report, a review of drugs that can prolong cardiac conduction interval does not list octreotide as a possible candidate (79).

In summary, octreotide may be a reasonable drug to try as adjunctive therapy postcoagulation or as primary therapy if other treatments are not feasible. There is a low rate of side effects with less serious outcome. However, despite reported success, there are no controlled trials of this agent. Similarly, it is unclear how long to continue therapy if success is achieved.

Other pharmacological agents use anecdotal reports and take advantage of various aspects of pathogenesis of AVMs. Early reports of therapy for watermelon stomach found, in two cases, 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 danazol 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 danazol 20 mg orally three times per day arrested bleeding in three patients within four weeks and

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 aminocaproic 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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