Title: Desmopressin in canine mammary carcinoma: comments on the importance of the administration route

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Several years ago, we proposed the hemostatic peptide desmopressin (1-desamino-8-D-arginine vasopressin; dDAVP) as a potential anti-metastatic agent to be used during surgical excision of locally advanced tumors. A prospective randomized study in 28 intact dogs with mammary carcinomas receiving perioperative intravenous dDAVP infusions (1 µg/kg) demonstrated a significant survival benefit in dogs with moderately (grade 2) or poorly differentiated (grade 3) tumors[1]. dDAVP is known to exert anti-proliferative and anti-angiogenic effects in laboratory models, by acting on AVPR2 vasopressin receptors present in tumor and endothelial cells. Moreover, dDAVP can induce the release of von Willebrand factor (VWF) from microvascular endothelium into blood circulation. Beyond its critical function in primary hemostasis, VWF plays a protective role against metastatic dissemination. An abrupt increase in VWF blood levels is able to interfere with the arrest of circulating cancer cells at target organs and also to induce apoptosis in micrometastatic foci[2].

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The article entitled "A prospective randomized trial of desmopressin in canine mammary carcinoma" recently published in *Veterinary and Comparative Oncology* by Sorenmo *et al*. retested dDAVP as a surgical adjuvant in 24 dogs with mammary carcinomas[3]. They reported that few dogs developed metastatic disease in this study, and no significant benefit of perioperative dDAVP administration was observed. We completely agree with the authors in the sense that subgroup comparisons between the high-risk subgroups were very underpowered, since none of the dogs with grade 2 tumors developed metastasis and only one dog with a grade 3 tumor was randomized to receive dDAVP[3]. More to the point, all intact dogs underwent ovariohysterectomy as part of their treatment in this study, thus reducing the risk of metastasis and possibly diminishing the impact of perioperative dDAVP on survival.

However, it is important to note that Sorenmo *et al.* used a nasal spray formulation of dDAVP administered by the subcutaneous route[3], instead of an intravenous infusion as in our previous study[1]. Even though subcutaneous administration is the standard of care in bleeding disorders, it was clearly demonstrated that dDAVP is ineffective by the subcutaneous route in experimental metastasis assays in mice. A clear dose-dependent anti-metastatic action was observed by using the intravenous injection (dDAVP doses ranging from 0.3 to 2 µg/kg), while no significant effects were obtained with similar doses by the subcutaneous route[4]. Although a hemostatic factor such as VWF is involved, anti-metastatic effects of dDAVP are not directly associated with the coagulation process[4]. VWF is a multifunctional protein and its role in resistance to metastasis is independent of its role in hemostasis[2], probably requiring the rapid peak concentrations associated with high intravenous doses to favor the elimination of early metastatic cells.

Finally, we agree with the authors in that a prospective randomized trial in dogs bearing grade 3 mammary tumors should be conducted with the aim of resolving discrepancies between studies. However, in order to confirm the therapeutic benefits of perioperative dDAVP, compound should always be administered using the intravenous route. In this setting, maintenance therapy based on additional postoperative doses of dDAVP, or its synthetic analog with enhanced cytostatic activity [V^4Q^5]dDAVP[5], could be used to consolidate the effect against dormant metastasis or disseminated tumor cells.

References

1. Hermo GA, Turic E, Angelico D, et al. Effect of adjuvant perioperative desmopressin in locally advanced canine mammary carcinoma and its relation to histologic grade. *J Am Anim Hosp Assoc* 2011;47:21-27.
2. Terraube V, Marx I, Denis CV. Role of von Willebrand factor in tumor metastasis. *Thromb Res* 2007;120 Suppl 2:S64-70.
3. Sorenmo K, Durham AC, Evans B, Scavello H, Stefanovski D. A prospective randomized trial of desmopressin in canine mammary carcinoma. *Vet Comp Oncol* 2020 doi: 10.1111/vco.12619.
4. Garona J, Pifano M, Scursoni AM, Gomez DE, Alonso DF, Ripoll GV. Insight into the effect of the vasopressin analog desmopressin on lung colonization by mammary carcinoma cells in BALB/c mice. *Anticancer Res* 2014;34:4761-4765.
5. Garona J, Pifano M, Pastrian MB, Gomez DE, Ripoll GV, Alonso DF. Addition of vasopressin synthetic analogue [V^4Q^5]dDAVP to standard chemotherapy enhances tumour growth inhibition and impairs metastatic spread in aggressive breast tumour models. *Clin Exp Metastasis* 2016;33:589-600.