



Q&A: EMERGING TOPICS

Electrochemotherapy for Companion Animals

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Abstract

Electrochemotherapy, a local treatment of various neoplasms, uses electroporation to change the permeability of cell membranes to facilitate the uptake of cytotoxic drugs. These drugs, injected directly into the tissue, would otherwise be unable to efficiently pass through the cell membrane. Electrochemotherapy has been shown to be an effective treatment for a variety of neoplastic processes and malignancies, sometimes in as little as a single treatment, with minimal to no side effects. It is best used to treat superficial tumors or areas where surgical excision was incomplete or could not be performed. Proper safety protocols must be used to protect the patient and veterinary team.



Take-Home Points

- Electrochemotherapy (ECT) can be a treatment option for many different malignancies and can provide an alternative treatment to surgery, radiation, and traditional chemotherapy.
- ECT can be a cost-effective option, sometimes requiring only a single treatment to obtain a complete response.
- Although ECT requires heavy sedation or general anesthesia, the procedure itself often takes 10 minutes or less, requiring minimal anesthetic time.
- ECT has minimal to no side effects.
- ECT requires minimal to no aftercare, easing owner burden.
- Electroporation not only facilitates ECT but can also be used for gene therapy and immunotherapy.

Electrochemotherapy (ECT) is an alternative treatment for superficial neoplasms in both human and veterinary medicine. ECT uses electroporation to change the permeability of cell membranes to facilitate the uptake of cytotoxic drugs. These drugs, injected directly into the tissue, would otherwise be unable to efficiently pass through the cell membrane. Bleomycin and cisplatin are the 2 most common drugs shown to be effective with this treatment modality, although other drugs are being researched. The mechanisms of action of ECT include

increased membrane permeability and intracellular drug accumulation, vascular effects, and involvement of the immune response.¹

ECT has been shown to be an effective treatment for a variety of neoplastic processes and to be completely effective in as little as a single treatment. It is best used to treat superficial tumors or areas where surgical excision was incomplete or unable to be performed. Side effects are typically limited to local tissue inflammation and necrosis. Performing ECT requires

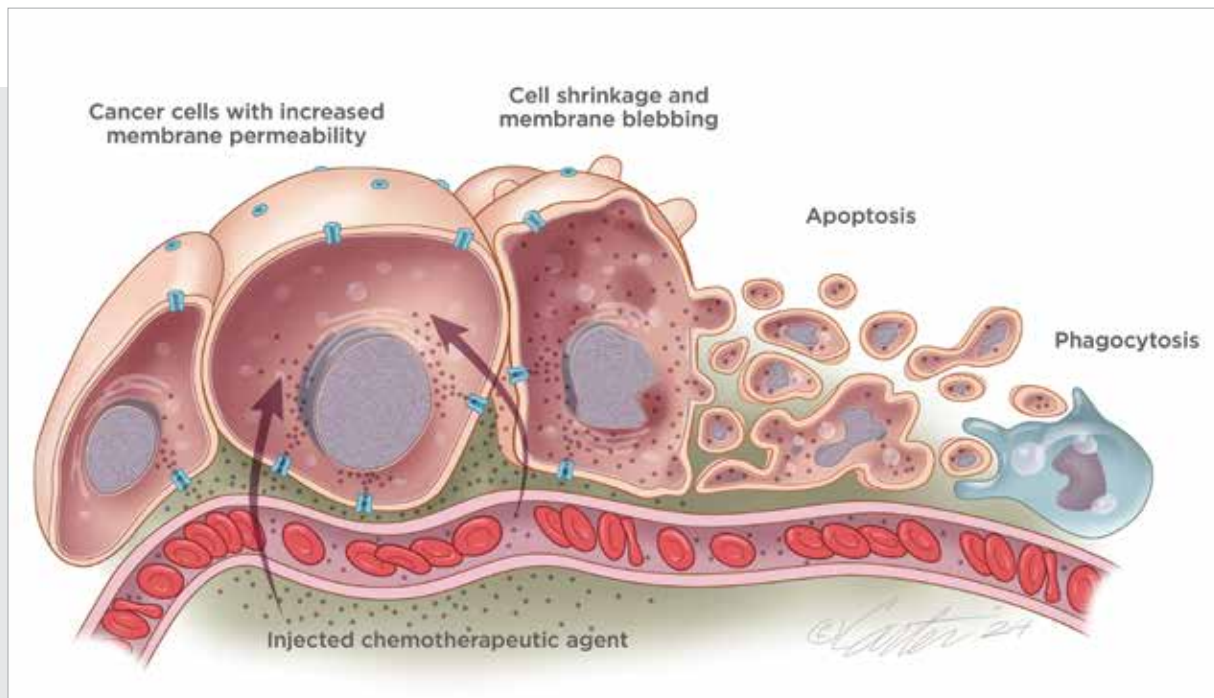


FIGURE 1. Applying the electrical pulse increases cell membrane permeability, allowing drug molecules outside the cell to enter quickly. The membrane permeability returns to normal immediately thereafter, containing the drug molecules inside the cell, where they can exert their action and cause apoptosis.



heavy sedation or general anesthesia. Proper safety protocols must be used to reduce risk of exposure and protect not only the patient but all staff involved. Overall, ECT can be an effective treatment for various malignancies with minimal side effects.

HOW DOES ECT WORK?

Electroporation is the process of introducing a substance into a cell using a pulse of electricity to temporarily open the pores in the cell membranes. Application of electrical current to the cell causes relocation of the charges on the cell membrane. This relocation of charges alters the cell's membrane potential, allowing the formation of pores through which water, charged molecules, and larger molecules may pass into the cell (**FIGURE 1**).

Various levels of electrical pulses have been studied, and a standard dose established of eight 1000 to 1500 V/cm 100-microsecond-long pulses.^{1,2} This process makes ECT successful. By allowing the drug to directly enter the cell, intracellular drug concentrations are 2 to 4 times higher than those seen with IV administration.²

Two types of electrodes are commonly used: plate and needle electrodes. Plate electrodes are appropriate for more superficial areas, while needle electrodes can reach deeper-seated tissue.

Vascular Lock

Vascular lock is the term used to encompass 2 vascular effects caused by the electrical pulses applied in ECT:

- Applied electrical fields assist stromal cells with drug uptake and affect endothelial cells of the tumor's vessels. This effect, termed *vascular disrupting effect of ECT*, leads to endothelial cell apoptosis and therefore disruption of tumor blood flow.

- The second effect is vasoconstriction in the area where the electrical field is applied.

These 2 effects combined “lock” the administered drug within the applied electrical field area, creating further exposure to the desired tissue. If a chemotherapeutic agent is administered after the electrical pulses are applied, it can block the drug from entering the tumor.¹

Immune Response

After ECT, tumors shed immense amounts of tumor antigen, which can induce a systemic immune response. This immune response can be upregulated by biological response modifiers such as interleukin-2, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor α .² Studies have shown a difference in the effectiveness of ECT between immunocompetent and immunocompromised patients. This difference implies that an immune response is key to ECT being a successful treatment.

WHAT ARE THE MOST UTILIZED CHEMOTHERAPY AGENTS?

Bleomycin

Bleomycin is an antitumor antibiotic. It exerts its action by inducing DNA strand breaks, although the exact mechanism of action is yet to be fully understood. Bleomycin is most commonly used in ECT because it has a higher potentiation of cytotoxicity when an electrical pulse is applied. Bleomycin can be given via the intratumoral (IT) and IV routes during an ECT procedure. Dosing parameters range from clinician to clinician, but a sufficient maximum dose of 15 U/m² per treatment is commonly used. Dilution of the bleomycin should be done according to manufacturer specifications. Depending on the size of the area being treated, most of this dose may be given intratumorally, with the remainder being administered intravenously. The IV administration should be performed before the IT injections due to the vascular lock effect. The IV portion of the drug, if applicable, should be given 4 to 8 minutes before the IT injections. Electrical pulses should be applied within 1 minute of the IT injections.

Cisplatin

Cisplatin is the second most commonly used drug in ECT. Cisplatin, a platinum-agent chemotherapeutic, binds to DNA and interferes with replication. Cisplatin

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is contraindicated in cats due to severe renal toxicity and typically fatal pulmonary toxicity. However, studies have shown that using cisplatin in ECT (rather than systemically) in cats results in mild toxicity concerns and positive treatment outcomes.³ Dosing parameters vary between clinicians, but a sufficient maximum dose per treatment is 15 mg/m². In dogs, the cisplatin dose may also be given intravenously and/or intratumorally, with IV administration occurring first.

WHAT CANCERS HAVE BEEN SHOWN TO BE RESPONSIVE TO ECT?

A variety of malignancies have been proven to be sensitive to ECT treatment on both dogs and cats. Anal sac adenocarcinoma, apocrine gland carcinoma, fibrosarcoma, localized lymphoma, mammary adenocarcinoma, mast cell tumors, melanoma, perianal tumors, and squamous cell carcinoma have all shown promising responses to ECT treatment. A meta-analysis of 1894 tumors from 44 eligible clinical studies published before October 2011 demonstrated that the effectiveness of a single-session ECT on cutaneous and subcutaneous tumors was 59.4% for complete response and 84.1% for objective response.¹

WHAT DOES THE ECT PROCEDURE INVOLVE?

ECT is a relatively quick, inexpensive treatment for a variety of tumor types. For the procedure, patients should be under heavy sedation or general anesthesia. Sedation or anesthesia induction and maintenance protocols may vary based on clinician preference. The patient should be positioned as necessary on a table that allows easy access for the anesthetist as well as the clinician and veterinary nurse. The clinician will be responsible for the IT injections as well as the application of the electrodes. The veterinary nurse assisting will be responsible for containing any rogue chemotherapeutic agent as well as operating the electroporator as instructed by the clinician. Isolation of the area being treated is necessary to prevent unnecessary drug exposure.

The area being treated should be clipped and scrubbed with aseptic technique with 1-cm margins around the treatment area. The chemotherapeutic of choice should be injected into the area of treatment to sufficiently encompass all potentially malignant tissue (**FIGURE 2 AND VIDEO 1**). Recall that any part of the drug to be given intravenously should be administered via that route before the IT injections.

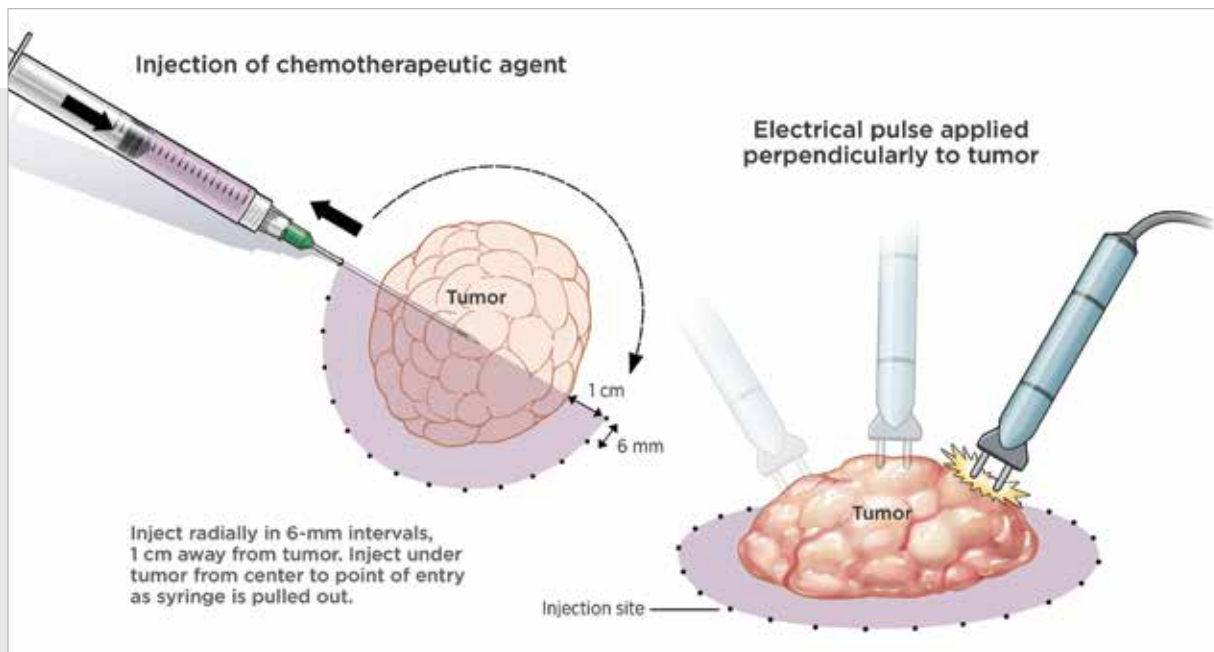


FIGURE 2. The injection of the chemotherapeutic agent should be performed at 6-mm intervals around the entirety of the site of the tumor with a 1-cm margin. When injecting, inject the agent while pulling out to deliver the drug to the entire 1-cm margin. After the injection of the chemotherapeutic agent, the electrical pulse is applied by the electrode in a perpendicular pattern around the treatment area.

**VIDEO 1**

The injection of the chemotherapeutic agent (in this case, bleomycin) is performed in a pattern around the area of interest. The incisional scar is being treated from an incompletely resected apocrine gland anal sac adenocarcinoma. Note how the bleomycin is being injected in a circular pattern around the scar line approximately 6 mm apart with 1-cm margins.

**VIDEO 2**

The electrical pulse should be applied in perpendicular pulses around the surface of the tumor/scar in 1-cm margins. Conducting gel is required with plate electrodes.

Once the chemotherapeutic has been adequately administered into the tissue, electrical pulses should be applied within 1 minute. For the use of plate electrodes, a water-based gel should be applied to the tissue in question before applying an electrical pulse. The application of the electrode should start from the safety margin of the tumor and progress toward the center in a circular motion. Applying the electrode twice in a perpendicular pattern will ensure the most complete application of the electrical field (**FIGURE 2 AND VIDEO 2**).

Gel application is not necessary when using a needle electrode. All needles should be inserted into the tissue to ensure proper electrical field application. The pattern described above for the plate electrode also applies to the needle electrode. The application of electrical pulses will cause a muscle contraction in the patient. Depending on the area of pulse application, measures should be taken to restrain the patient's body to protect the patient and those around it.⁴

HOW DO I KEEP MYSELF AND OTHERS SAFE DURING ECT?

As with all chemotherapy administration techniques, extreme care must be taken to protect all people involved in the procedure from exposure to the drug in question. Full personal protective equipment must be used. This includes a nonpermeable gown, double-

layered chemotherapy-approved gloves, eye protection (preferably goggles and a face shield), and at least an N95 filter mask (**FIGURE 3**). The procedure should take place in a dedicated chemotherapy administration suite, as contamination risks are high. Ideally, the suite should have negative air pressure to prevent flow of contaminated air into other parts of the building. Chemotherapeutic agents should be prepared in a class II laminar flow biological safety cabinet to collect any aerosolized particles produced during preparation.

The area of the patient's body being treated should be isolated as much as possible using nonpermeable chemotherapy pads, gauze, or other absorbent material



FIGURE 3. Full personal protective equipment must be used during electrochemotherapy. This includes a nonpermeable gown, double-layered chemotherapy-approved gloves, eye protection, and at least an N95 filter mask.



to collect any leaking chemotherapeutic agent. The clinician should take care to limit unnecessary injection, leakage, or spray of the chemotherapeutic agent. All disposable materials used during the procedure should be discarded in an appropriate chemotherapy waste or sharps container. After use, tools such as the electroporator, anesthetic machine, and monitoring equipment should be thoroughly wiped down with bleach wipes or a specific solution recommended by the equipment's manufacturer. Tools or contaminated surfaces should not be sprayed directly as this could potentially cause aerosolization of chemotherapeutic agents. The patient's treated area should be cleaned thoroughly once ECT therapy has been completed to ensure that no residual contamination is present; chlorhexidine scrub/solution and alcohol are commonly used.

If a person is exposed to a chemotherapeutic agent or if a contaminated needlestick occurs, flush the area copiously with water and seek medical attention as needed. Bleomycin and cisplatin rarely cause acute effects with skin surface contamination, although irritation may occur.⁴ Every safety measure should be used to prevent any exposure to these agents as long-term exposure has been linked to a variety of significant medical issues.

With the use of electricity, it is also vital to ensure that the patient is not directly on a metal table and that no metal is touching the patient when the pulse is applied. Care should also be taken to not have any personnel touching the patient while the electrical pulse is applied. If restraint or particular positioning is required, tools such as gauze, slip leads, or other nonmetal devices should be used.

WHAT DO I NEED TO DISCUSS WITH CLIENTS AFTER PERFORMING ECT?

Aftercare for ECT patients is minimal. Educate clients about postsedation/anesthesia complications and monitoring. Discuss potential side effects, including pain, inflammation, tissue necrosis, and wound formation, although these side effects are uncommon. Inform clients that they should avoid touching the treatment site for 24 to 48 hours to avoid any potential exposure to chemotherapy agents lingering on the skin.

WHAT OTHER TREATMENTS CAN ELECTROPORATION PROVIDE?

Gene electrotransfer uses electroporation to deliver a DNA plasmid, oligonucleotides, and short RNA molecules into the cell. This is a significant progression in both human and veterinary medicine, as it allows a nonviral delivery method for gene therapy and immunization. Gene electrotransfer has been studied for diseases such as cancer as well as autoimmune and inflammatory disorders.⁵ **TVN**

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Brooke has been a certified veterinary technician for more than 13 years and a veterinary technician specialist in oncology for more than 5 years. She currently works as the clinical education specialist for WestVet Emergency and Specialty Center. Brooke is passionate about educating fellow veterinary nurses and clinical team members, with a special interest in oncology, specialized procedures such as electrochemotherapy, and compassionate client care. She regularly presents continuing education courses on local and national levels for various companies and conferences, contributes to textbooks relating to oncology, and writes articles for veterinary journals.