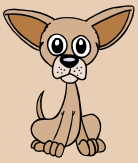
OUCH-Y CHIHUAHUA THAT HURTS!



INSIDE PMB

February 2008

REGISTRATION COORDINATORS

Tired of finding investigators' registration forms buried like old bones on their desks right before their registrations expire? CTEP allows 'Registration Coordinators' to receive all their investigators' annual registration forms directly. For more information, please E-mail ctepreghelp@mail.nih.gov with the subject "Make me an RC."

Questions about Investigator Registration (IR) requirements, statuses, or any registration-related issue? The first available member of our IR team will bark back right away! E-mail the PMB Team at pmbregpend@ctep.nci.nih.gov .

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OUCH-Y CHIHUAHUA!

When you need an expression of dismay, annoyance, or resignation, our neighbors to the south have a good one: "Ay, chihuahua!" What's it mean? This colloquialism is like "Holy Cow!" or "Geez Louise!" Older readers may remember a certain Bandito who was always uttering "Ay, chihuahua!" when he ended up in the doghouse.

We've adapted this saying for this issue of INSIDE PMB, which addresses pain in a number of different ways.

EXCURSIONS

If you inadvertently store a PMB-supplied agent outside of its normal storage conditions, call PMB before returning it to us. We might have unpublished data to support its continued use, and you can whippet into the fridge or komondor someone else to put it back on the shelf. If approved by PMB, continued use of the agent does not constitute a protocol violation.

That said, please do not even begin to think that today's excursion data is good tomorrow. You have to hound us for current data each time an excursion occurs.

OUCH-OUCH-OUCH-Y-CHIHUAHUA

Type of Pain	Presentation	Examples of cancer related causes
Bone pain	•Ranges from dull to deep and intense •Usually localized •Intensifies with movement or at night •Usually in the long bones of the upper arm and upper leg, or major bones (pelvis, hips, and spine)	Metastasis, often from breast, prostate, or multiple myeloma, lung or colon cancer
Colic pain	•Transient cramping	Post-operative complications, antineoplastic-induced adverse events, kidney metastasis
Muscle pain	•Soreness, stiffness, or cramping •May mask bone pain as surrounding muscles contract involuntarily	Infiltration or occlusion of blood vessels, adverse events of drugs, like myalgias and arthralgias subsequent to taxanes
Neuropathic pain	•Constant superficial burning, varying with the degree of nerve compression or infiltration •Risk increases in patients taking neurotoxic agents like metronidazole or isoniazid •Occurs more frequently in individuals with diabetes, alcoholism, or severe malnutrition	Tumor infiltration or compression of nerves. Sub-types include peripheral neuropathy that can follow vinca alkaloids or the palmar-plantar erythrodysesthesia associated with paclitaxel, fluorouracil, capecitabine or cytarabine. Sorafenib and sunitinib, too!
Pleuritic pain	•Pain on inspiration	Adverse effect of antineoplastic therapy or disease-related progression
Visceral pain	•Pain at the tumor or injury site •Pain referred to somatic area supplied by same vasculature	Tumor growth or veno-occlusion

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STRAY NEWS

Oxaliplatin (NSC 266046): Some formulations and strengths of oxaliplatin have become as scarce as Alpha Blueblood Bulldogs, so periodically, PMB will provide whatever's available: powder or liquid. Your protocol has instructions for both. The manufacturer is in heat, and we expect whelping of oxaliplatin puppies in the prime birthing season: spring. Please submit Clinical Drug Requests as usual and PMB staff will adjust them as needed.

CCI-779 (temsirolimus, NSC 683864): Please paws and contemplate before you attempt to transfer temsirolimus. Some NCI studies will be using commercial Torisel and others will be using the investigational agent, and they have different mixing instructions. Studies using commercial drug cannot transfer agent to studies using investigational drug and vice-versa. Please call PMB for approval before transferring CCI-779.

RED LIGHT: HEEL! GREEN LIGHT: GO!

PMB is gathering ideas and pilot-testing new processes that save paper and energy. We'd love to hear how your offices have reduced consumption and waste. Send your "going green" ideas and successes to pmbafterhours@mail.nih.gov with the subject line "GREEN IDEAS."

D-D-D-DARF UPDATE

PMB customers use the Drug Accountability Record Form (DARF) to record receipt and document dispersal of investigational agents. The United States Office of Management and Budget (OMB) requires review and re-approval of the form every three years. Our team manager started this process in December 2006, but OMB has yet to approve the form. Until you receive official word, continue to use the existing form that has an 11/2007 expiration. We'll post the newly approved DARF on the CTEP web site as soon as it's available, and notify you via this newsletter.

PMB now uses the word "agent" to encompass drugs and biologics. Thus, we think that this form should be called an Agent Accountability Record Form. That would be an AARF, wouldn't it?

BARKING UP THE WRONG TREE!

DON'T EVEN TRY TO ORDER:
- Bevacizumab (open label) 100 mg vials
- Bevacizumab 1000 mg vials
- COL-3 10 mg capsules
- Dasatinib 70 mg tablets
- Irinotecan 40 mg vials
- STI-571 (imatinib) 100 capsules
- Tirapazamine 175 mg vials

These strengths or formulations are no longer available from PMB.

THIS BRINGS OUT THE JUNKYARD DOG IN US:

- Ordering more than an 8 week supply. Don't. Please don't. Grrrrrrrr.
- Putting ASAP in the "date needed" field. ASAP is subjective. Please provide a specific date so we will prioritize the workload and get you the agent that you need when you need it. If we can't make the date you put, we'll give you a call.
- Ordering by patient on open label protocols. On a single open label order, order an eight week supply of agent for all patients on that protocol. We do not want to see weekly orders from your site for the same agent on the same protocol.

CONTEST WINNER

PMB half-heartedly congratulates Al Donner in New York, our latest PMB newsletter contest winner. The college football season had some unbelievable ups and downs. Almost every team proved itself undeserving for the NCAA college football championship game, so it was remarkable LSU and Ohio State went to the National Championship Title on January 7. Al Donner picked LSU and Oregon (which explains our half-hearted congrats). We'll send Al half of the normal prize of cookies or dog biscuits. Special recognition to Toni Sinclair in Houston, who won the other half.

ANOTHER DOGGONE CONTEST

1. What is the dog dose of aspirin?
a. two tabs now, call the vet in the morning
b. between 5 and 15mg/lb every 12 hours
c. aspirin is toxic to dogs

2. CYP2D6 is expressed at a low level in human liver, but is involved in the biotransformation of 30% of marketed drugs. What CYP enzyme in dogs has enzymatic activity similar to humans' CYP2D6?
a. It's the same as humans; that's why we test drugs in dogs.
b. CYP2D17
c. CYP2D15

3. Dogs sometimes experience "wind-up"—heightened sensitivity that alters peripheral and central pain thresholds—similar to human referred pain. What reduces wind-up?
a. amantadine
b. gabapentin
c. ketamine
d. all of the above

Send your answers to pmbafterhours@mail.nih.gov and we'll enter your name into the quarterly drawing for cookies or dog biscuits, all homemade!

DON'T HOWL AT THE MOON! SEND AN E-MAIL!

Sally had a serious bone to pick
With whoever had left her up a crick.
Saturday night--
No sunitinib in sight.
Time to teach an old dog a new trick!

Wondering if anyone ordered more agent, or if we've shipped it yet? Have a question about agent availability, the best way to get agents fast, or if an order was even ever faxed, and want the answer in writing? E-mail pmbafterhours@mail.nih.gov. Expect an answer on the next

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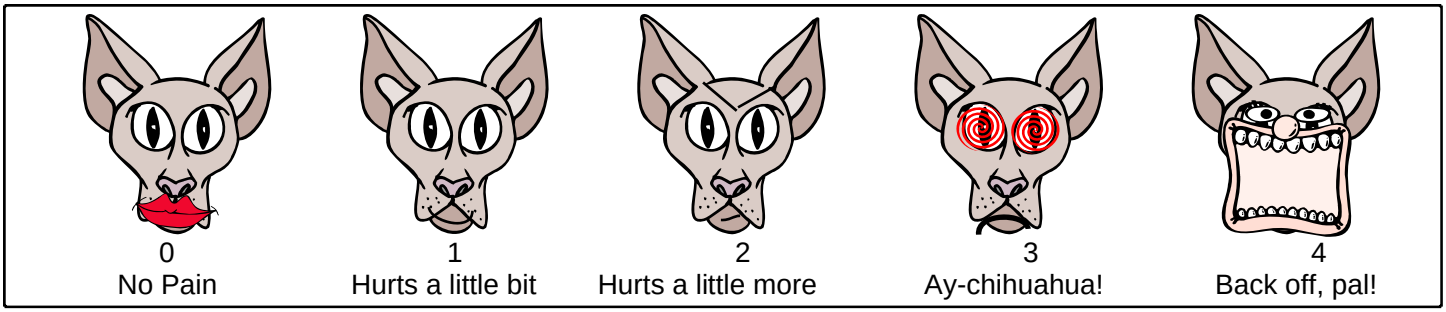

ARE YOU HAVING ANY PAIN TODAY?: A QUICK REVIEW

By now, we all know (or should know) that pain is subjective—we know it's present only by patient self-report. Unfortunately, some patients are unable to report pain. Clinicians use other measures to detect pain and evaluate interventions, but assessment strategies like interpretation of behaviors or proxy pain estimates are insufficient when used alone.

Pain assessment tools help health care providers diagnose and measure pain intensity, and help patients describe the quantity or intensity of the pain. Several single item pain scales are common:

•The visual analog scale (VAS) is a line, usually 100 mm long, with its ends labeled with pain intensity extremes (eg, no pain, extreme pain). Patients mark the line at the spot representing pain intensity. The distance from the "no pain" end to the mark is their score.

• Numerical rating scales (NRS) use a range of numbers, usually 0 to 10 with the lowest number representing no pain, and the highest representing excruciating pain. Our pain scale, above, uses 0 through 4, and you may use it, as it is in the public domain.

• Verbal rating scale (VRS) list descriptors or phrases (none, some, moderate, severe) representing pain intensity. Patients select the single word or phrase that best represents their pain level; each word or phrase has a number associated with it (None=0, severe=3).

• Pain face scales employ drawings of facial expressions representing increasing levels of pain intensity and suffering. Patients select the drawing that best represents their pain level.

A multiple item measure of pain intensity, the brief pain inventory (BPI), averages current pain and worst, least and average pain during a specified period (usually the past week) into a single pain intensity score.

Valid, Useful, Reliable?

In any type of pain, pain scales should be valid indicators of pain or useful predictors of outcomes like quality of life. They should also be reliable—providing scores free of measurement errors. Many factors can influence the patient's response to a pain scale: the assessment setting, the person administering the measure, other subjective experiences and feelings, or even motivational factors. Some measures may be difficult for patients to understand, especially if they have limited cognitive abilities.

The VAS consistently demonstrates sensitivities to cancer pain associated with treatment or time and usually shows strong associations with other pain intensity ratings, performance status, diagnosis, setting (inpatient or outpatient), psychological distress and global quality of life measures. It also shows test/re-test reliability. The VAS may be more difficult than other pain ratings for patients to understand and complete. One study found that 16% of patients are sometimes unable to complete a VAS even with nurse assistance, and this number increases to as much as 84% as disease progresses.

Studies support validity and reliability of NRS scales. NRS scales are sensitive to changes in pain associated with radiotherapy and physical therapy and pain treatment. Its associations with analgesic medication use, perceived need to contact health care providers, pain interference, dyspnea, and other symptoms like nausea, dry mouth, anorexia, fatigue, constipation, treatment satisfaction and global quality of life demonstrate validity. Test-retest validity was very stable for NRS ratings of worst pain and average pain, but not for current pain.

The VRS is sensitive to changes in pain with treatment and shows strong associations with other measures of pain intensity, such as survival, tumor size, analgesic use, disease stage, and anxiety about pain. Test retest reliability is unproven.

Limited information is available in cancer patients on pain face scales reliability and validity. The pain face scales show strong association with pain intensity and 81% of patients were able to complete the face scale. One study noted that male patients were uncomfortable with rating their pain at the highest level because the expression representing the most severe pain had tears on the face of the drawing. Thus, this scale may underestimate pain intensity in some patients with severe pain. Clinicians may consider using PMB's tear-free faces scale for those growling sires, but see our disclaimer below.

Studies have shown that the BPI scale is highly internally consistent and relatively free of cultural and linguistic bias. It is associated with other measures of pain intensity, performance status, pain interference, source of assessment, and nationality. No study has examined the BPI Pain Intensity Scale's sensitivity to the effect of cancer pain treatment.

Commonly used single-item pain intensity ratings are valid and adequately reliable as pain intensity measures. Some scales are easier for cancer patients to understand and use. Multiple item measures are reliable, but evidence concerning their validity is lacking. And our pain scale? Disclaimer: We have no idea if it's reliable or valid, but it is kind of a howl, isn't it?

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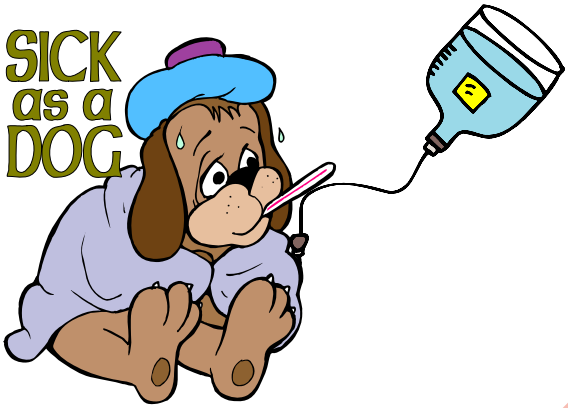


EXTRAVASATION MANAGEMENT: INVESTIGATIONAL CHEMOTHERAPEUTIC AGENTS

Although nurses are at the forefront of extravasation prevention and management, pharmacists are often consulted when an extravasation occurs. With many commercial chemotherapy agents, little evidence supports clinical decisions. Even less is available for investigational agents; thus, all investigational chemotherapeutics should be treated as potential vesicants.

If extravasation of an investigational chemotherapeutic agent occurs, consult your institution's extravasation policy for "other agents." It may describe stopping the infusion immediately, but perhaps leaving the needle in to withdraw blood and remove some of the drug before removing the infusion needle, estimating the amount of extravasated solution, elevating the extremity for 48 hours, and/or applying ice or warm compresses. (Never use cold for vinca alkaloid extravasation.) Contact PMB to see if the manufacturer has any recommendations. And, most importantly, be sure to report any adverse reactions appropriately.

Preclinical data in animals may reveal increased tissue necrosis or inflammation with indwelling catheters but the true picture is not apparent until the agent reaches the clinic. After reports of extravastion in humans, manufacturers may implement preventive strategies earlier. This may involve slowing the infusion rate or, for example, in the case of ispinesib (SB-715992, NSC 727990), adding a 2nd line (via Y-port) infusing D5W; this dilutes the agent as it infuses.

Even after increased reports, some agent's extravasation management guidelines may be unclear. For example, the literature describes oxaliplatin as both an irritant and a vesicant. Application of heat has helped some patients, whereas cold has aided others. Patient improvement occurred after no antidote in some cases and after 0.16 molar sodium thiosulfate administration in others. Single literature citations are insufficient as a basis for extravasation management. A multidisciplinary approach including nurses, physicians, and pharmacists is warranted. Please report extravasation when it occurs, and document its occurrence clearly in the patient's clinical record.

RECALL REACTIONS

Radiation recall, recall inflammatory reactions, or recall dermatitis are acute inflammatory reactions in previously irradiated or extravasated areas after the administration of certain systemic agents. The reaction occurs frequently on the skin, but it may also be seen in the oral mucosa, larynx, esophagus, small intestine, lungs, muscle tissue, and brain. Most, but not all, drugs associated with recall reactions are cytotoxics, and the reaction may occur even if a different infusion site is used. No one knows why this happens. Recall reactions may occur days to years after radiation or extravasation. Discontinuation of the inciting drug and the use of corticosteroids or nonsteroidal anti-inflammatory agents is the usual treatment.

Extravasation (ek-strav"ə-sa´shən) is technically a discharge or escape of blood or some other fluid normally found in a vessel or tube, into the surrounding tissues. Urine and blood can extravasate, too. Chemotherapy extravasation may lead to persistent pain, burning, stinging, and erythema at the injection site or along the course of the vein, and sometimes, progressive tissue damage. Debridement and excision of necrotic tissue should be considered if pain continues for 1-2 weeks.

Did you say "preclinical," as in animal studies? Most preclinical studies that look at extravasation are conducted in rodents, not dogs.

Speaking of "preclinical," dogs have a long history in biomedical research, strong anatomical and physiological similarities to humans, and pet dogs are often diagnosed with cancer--AY, caramba! More than 1 million are diagnosed with cancer annually in the United States. This has focused cancer researchers' interest on the dog. They've conducted studies in dogs with cancer to answer questions about human cancer therapy since the early 1960s.

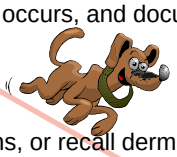
One species irritant is another species joy. Barking for example. Or garbage.

PAINFUL WORDS GONE!

For several years now, this paragraph has appeared in all protocols using bevacizumab (NSC 704865):

The bevacizumab to be supplied for this protocol is intended for clinical trial use only and is not the commercially available Avastin. Investigational bevacizumab and commercially available Avastin may be produced at separate facilities and some difference may exist between the two products, although both are required to meet similar product testing criteria and are expected to be very similar in safety and activity. For further details and molecule characterization, see the updated bevacizumab Investigator Brochure.

We have been officially notified that we can remove this language from protocols, and similar language from the consents.



Did you say, "mutt-i-disciplinary"? Have you considered putting Fido on your team? Consider comparative oncology. Comparative oncology integrates study of naturally occurring cancers in animals, especially companion animals (mutts or purebreds, not laboratory-bred dogs) into studies of human cancer biology and therapy. Cancers in companion species are well suited to investigations of cancer biology and drug development. The germline genetic diversity of a population of dogs (from Chihuahua to Great Dane) with a given cancer is similar to the diversity seen in a well-mixed population of humans with a given cancer. For many gene families, especially those associated with cancer, the canine genome is much closer to the human genome than that of mice. The genetic molecular alterations that drive cancers in dogs and humans are similar. Sadly, this field hasn't developed very quickly, but interest is very high right now.