Curcumin Monograph for Intravenous Use

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INTRAVENOUS CURCUMIN:

Abstract: Intravenous curcumin is a novel and promising adjunct to the care of the cancer and chronically ill patient population. Oral administration has been shown to provide some benefit, but absorption and distribution kinetics do not always allow maximal benefit.

A review of over forty peer-reviewed publications by the author as well as personal use of intravenous preparations of curcumin in well over one thousand high dose infusions [8] yields this summary and rationale for the use of intravenous curcumin.

Of particular note to the health care provider desiring to employ intravenous curcumin: This parenteral product is not like the common water soluble nutrients and drugs infused and extreme care and caution must be employed when ordering and infusing it. The dose, form, administration and other guidelines set forth below must be followed to avoid adverse events.

FORMS OF THE MEDICATION: [8]

A significant difficulty in describing the infusion of curcumin is the variety of potential forms of infusion product compounded. This paper describes mainly the emulsion form (number 3 below). We have additionally infused form "2" below and find it more phlebogenic. No extrapolation of the clinical data presented herein should be made to forms other than the curcumin emulsion form (number 3 below).

[1] Lipid (in a phospholipid Liposphere). Very hard to compound properly and may be quite effective. Dripped slow like phosphatidylcholine IV.

[2] Curcumin in Cyclodextrin. Faster administration is possible but still a phlebitis potential if run too quickly. Our clinical experience points to the possibility that at higher doses this form is less efficacious in advanced cancers than the emulsion form below. [8]

[3] Curcumin emulsion: Stabilized with a non-bound agent for solubility. Infusion rate is slow but is very vein tolerant. We are running kinetic studies now and have a few very positive outcomes. This is the form we currently infuse.

[4] Water soluble solution. Highly alkaline to the point if not dilute will cause significant phlebitis and pH changes.

INTRAVENOUS USE GUIDELINES:

Dose:

- Test dose at 1 to 10 mg/Kg IV on the first day [1,8]
- Subsequent doses could increase to 40 mg/Kg if tolerated two to three times weekly [1,8].
- For cytokine manipulation, autoimmune cases and potentially pain cases we find the following doses useful:
    - 1.5 – 10 mg / Kg
- For advanced cancer we have found much higher doses required. In the cases where we have had tumor response with curcumin as primary therapy we find the following doses useful:
    - Test doses at 5 – 10 mg / Kg then escalate
    - Top end doses have required 30 – 40 mg/Kg for tumor response

Administration:

- Intravenous dosing via either a central or peripheral line.
- Carrier solutions:
    - Dextrose 5% in Water (D5W)
    - 0.9% normal saline may be an appropriate choice based on compounding pharmacy advice
- Dilution:
    - Many of the adverse reactions appear to not occur with better dilution of the curcumin.
    - Our experience has shown that curcumin should not be administered at a lower dilution than 100 mg in 100 mL of saline or D5W.
    - Most patients tolerate 400-500 mg in a 500 mL IV bag / 800 – 1000 mg per 1 Liter bag.
    - Rate of administration: 10 mg/min max until tolerance is established
- Rate of administration:
    - Speed is variable and based on patient tolerance.
    - At 20 – 40 mg / Kg doses we find the following:

        - At the above dilutions the first IV should run at 5 to 7 mL / minute.
        - If tolerated then a rate of 7 – 10 mL / minute is often tolerated.
    - At low dose (500 mg or less) we find:
        - Most doses 50 – 500 mg are given in 500 mL IV
        - At this dose we run the IV at 7 - 10 mL / min.

- Other IV compatibility:
    - No other additives should be mixed in the IV bag with the curcumin and carrier solution unless approved by the compounding pharmacy.
    - Vitamins, minerals or other antioxidants in a separate IV – same day is acceptable.
- Other IV incompatibility:
    - Oxidative treatments including IV Ascorbate over 20 grams – separate by 24 hours

Screening:

- Intolerance to oral curcumin excludes use in the IV setting
- Lab studies:
    - CBC, Chemistry panel (Metabolic panel including electrolytes, bilirubin, AST/ALT, eGFR/BUN/CRE)

Observed Reactions: [8]

- No anaphylactic or anaphylactoid observed to date.
- Nausea and vomiting:
    - In a minority of patients receiving over 10 mg/kg doses a transient and self-limited syndrome of dizziness, nausea and often vomiting has been observed. In each case the patient observed a dizziness and nausea combination of symptoms followed by vomiting of what appeared to be bile within 2-4 hours of finishing the infusion.
    - In each case the patient reported feeling “much improved” after the vomiting.
    - The vomiting was limited to one session following the infusion.

  - No patients have elected to discontinue high dose curcumin IV due to this experience.
  - In each case the nausea and vomiting was either a lone event or two events in a row and were not at the beginning of therapy (most were after three to five infusions). Most only happened once.
  - Our approach has been to decrease the body weight dose and ramp back up again to the therapeutic dose if tolerated.
  - The proposed mechanism based on patient observations and clinical correlation is an aggressive choloretic effect sometime after the initiation of the infusion series that leads to increased biliary activity, nausea and the other symptoms.
  - We do now recommend that patients consume a fiber supplement for bile sequestration before, during and the evening of the infusion. Psyllium husk at 5-10 grams per dose or cholestyramine at 2-4 grams per dose (all usual dose and administration cautions observed). This is to be done without fail for every IV of curcumin given.
  - Although only one in 30-50 infusions at doses over 10 mg/kg have reported this occurrence it is advisable to notify patients of the possibility in higher dose infusions and take preventive precautions (hydration and oral bile sequestrants).

- Some transient 'manic' / euphoric symptoms during and after the IV for up to 2-4 hours in a minority of patients.
- Peripheral heat and hand foot itching has happened at doses above 20 mg/mL in a minority of patients. Duration of 1-2 days.
- Transient (lasting seconds to minutes) central chest heat feeling.
- Skin rash, redness, dizziness all reversed with a hydration IV of 500 mL NS
  - Protocol is to stop the curcumin infusion and start the NS IV via piggy-back line. Infuse until the reaction stops and then (in most cases) re start the curcumin at a slower rate.
  - These patients will require a higher dilution on their next curcumin infusion.

Cautions:

Curcumin is a GRAS (generally recognized as safe) food additive by the FDA. Multiple studies using

High doses of oral curcumin in humans have shown incredible safety [2,3,4].

Potential cautions (not contraindications) include:

- Patients who exhibit any Type-1 / IgE symptoms post – test IV dose
- Patients on **anticoagulants** [5]:
    - Employ caution in dosing and monitor for increased bleeding.
- Patients with known **gallbladder disease** [6-8] or Patients who develop post-IV diarrhea:
    - Question patients. Increased right upper quadrant or right shoulder pain, or significant post-IV diarrhea may indicate a decrease in dose or discontinuation of therapy.

Use in marginal liver or kidney function:

It should be noted that any IV therapy can present a transient stress on the kidneys or liver. In the presence of other factors (such as chemotherapy and dehydration) this can be additive in stressfulness to these organ functions.

At this point I have ordered and supervised over 5000 doses of IV curcumin (and monitored for adverse events another 5000 doses) in humans. The following recommendations are based on that experience.

Important note regarding form and dose of IV curcumin:

These observations and recommendations only relate to the emulsion form of IV curcumin, and only relate to proper administration rates and dilutions as set forth above. Note that "high dose" is 10 – 40 mg/Kg and "low dose" is 1 – 10 mg/Kg. High dose is reserved for advanced cancers and low dose used in autoimmunity, inflammatory conditions, kidney disease etc.

Hepatic effect observations:

It should be noted that curcumin is recognized as both hepato-protective and hepato-restorative. [9,10] Observations of transient elevations in AST and ALT and changes in lipids are common in higher doses (over 10 mg/Kg). In advanced cancers these changes have never necessitated discontinuation of therapy nor had any long term negative health outcome associated with them. Many theories exist as to why these transient changes occur, but are only theories as the use of high dose IV curcumin is

recent. This is keeping in mind that the dosing range of 10 – 40 mg/Kg which is likely to produce such hepatic effects is exclusively reserved for advanced cancer therapy.

We have not noticed any of these hepatic effects in low dose (1 – 10 mg/Kg) IV curcumin.

Renal effect observations:

Curcumin is well studies in animal and human models to be nephro-protective and even nephro-restorative. [10-16] Unlike the hepatic effects noted above we have not observed any renal function decrease in low or high dose IV curcumin use ***when used per the monograph.*** Renal impairment is more of a potential (although rarely noted clinically) concern with high dose IV curcumin and should be monitored as noted below.

Clinical Recommendations:

Hepatic function adjustments:

In low dose IV curcumin we screen hepatic functions only if indicated, but low dose IV curcumin rarely deranges liver function testing.

However our general clinical guideline is to notify the patient and other practitioners that hepatic function (including lipid) changes will likely occur during high dose IV curcumin. As stated above we have not seen any comorbidity as a result of these hepatic lab changes. Additionally as we are treating generally high stage / grade cancers that are non-responsive we rarely adjust the IV curcumin dose, but we do monitor lab changes. We have seen some cases where the lab changes reverted to normal with a lower (but still potentially therapeutic) dose of IV curcumin and if the lab changes are of concern to patient or practitioner we will lower the dose while notifying the patient that the efficacy may be lower at lower doses.

Renal function based screening:

The standard screening I set for the NIH and other research studies is as follows:

eGFR	IV Rx.	Frequency of re-testing
>60	*Standard	every 4-6 weeks

40-60	*Standard	every week until proven stable
21-40	**Modified	36-48 hours post every IV until proven stable
<20	Low dose curcumin, Hydration or QOL formulas only	

*Standard high dose is 10 mg/Kg escalating to therapeutic dose between 20 – 40 mg/Kg

** Modified dose is generally 1 – 10 mg/Kg while tolerance is noted

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Assessment of dose adjustment in a patient with decreased eGFR:

The only way to assess dose effect in the patient with eGRF <40 is a therapeutic trial. Below is our standard protocol which has proven safety and efficacy in over 1000 cases:

1. Patient has baseline labs drawn (or patient on active therapy has an eGFR drop below 40).
2. Patient has 1-3 IV infusions at the lowest end of the body weight dose (Range is 1 to 10 milligrams / kilogram body weight) these infusions are dosed at 1, 3 then 5 milligrams per kilogram body weight.
3. Labs are re-run (never draw electrolytes or kidney function labs directly following a curcumin IV. Our standard is at least 36 – 48 hours following a curcumin IV).
4. If labs are stable or improved IV infusions progress with predetermined monitoring and normal dose escalation.
5. If labs worsen then a clinical decision is made as to risk-benefit of infusion and monitoring frequency required to keep the therapy safe.

SELECTED LITERATURE SUMMARY:

Mechanisms of Action:

From the Abstract (Anand):

Curcumin is a diferuloylmethane derived from the Indian spice, turmeric (popularly called ‘‘curry powder”) that has been shown to interfere with multiple cell signaling pathways, including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and down-regulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR 4) and inflammation (NF-jB, TNF, IL-6, IL-1,

COX-2, and 5-LOX). The activity of curcumin reported against leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma reflects its ability to affect multiple targets. Thus an ‘‘old-age” disease such as cancer requires an ‘‘age-old” treatment.

From the Conclusions (Gupta):

In this review, we have thus made an attempt to compile all the experimental and theoretical studies on the interactions of curcumin with various targets. As is clear from this compilation, curcumin is effective against a variety of inflammatory ailments and modulates multiple cell signaling pathways. Curcumin’s ability to bind to carrier proteins improves its solubility and bioavailability. Most of the biomolecules that curcumin binds to are integral components of cell signaling pathways and therefore may be pharmacologically relevant. However, most of the direct interaction data obtained to date are based on in vitro studies.

From the Abstract (Reuter):

Epigenetic regulation, which includes changes in DNA methylation, histone modifications, and alteration in microRNA (miRNA) expression without any change in the DNA sequence, constitutes an important mechanism by which dietary components can selectively activate or inactivate gene expression. Curcumin (diferuloylmethane), a component of the golden spice Curcuma longa, commonly known as turmeric, has recently been determined to induce epigenetic changes. This review summarizes current knowledge about the effect of curcumin on the regulation of histone deacetylases, histone acetyltransferases, DNA methyltransferase I, and miRNAs. How these changes lead to modulation of gene expression is also discussed. We also discuss other nutraceuticals which exhibit similar properties. The development of curcumin for clinical use as a regulator of epigenetic changes, however, needs further investigation to determine novel and effective chemopreventive strategies, either alone or in combination with other anticancer agents, for improving cancer treatment.

Indications for IV Use:

From Anand p.141:

Two in vivo studies were reported showing the antitumor activity as well as chemosensitization effect of curcumin against pancreatic cancer. In a xenograft model study, pancreatic cancer cells were injected subcutaneously on the side of the abdomen of female nude mice. Once tumor masses became established, animals were randomized to receive intravenous liposomal curcumin (40 mg/kg, 3 time per week) for 20 days. Treatment with liposomal curcumin resulted in reduced tumor size and visible blanching of tumors showing decreased expression of CD31 as well as VEGF and IL-8. These results indicate that curcumin suppressed pancreatic carcinoma growth in murine xenograft models and inhibited tumor angiogenesis [L. Li, F.S. Braiteh, R. Kurzrock, Liposome encapsulated curcumin: in vitro

and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis, Cancer 104 (2005) 1322–1331.] and [N. Dhillon, B.B. Aggarwal, R.A. Newman, R.A. Wolff,A.B. Kunnumakkara, J.L. Abbruzzese, D.S. Hong, L.H. Camacho, C. Ng, R. Kurzrock, Curcumin and pancreatic cancer: phase II clinical trial experience, J. Clin. Oncol. 25 (2007) 4599.]

From the Abstract (Chen):

Curcumin is a multi-functional and pharmacologically safe natural agent. Used as a food additive for centuries, it also has anti-inflammatory, anti-virus and anti-tumor properties. We previously found that it is a potent inhibitor of cyclosporin A (CsA)-resistant T-cell co-stimulation pathway. It inhibits mitogen stimulated lymphocyte proliferation, NF@kB activation and IL-2 signaling. In spite of its safety and efficacy, the in vivo bioavailability of curcumin is poor, and this may be a major obstacle to its utility as a therapeutic agent. Liposomes are known to be excellent carriers for drug delivery. In this in vitro study, we report the effects of different liposome formulations on curcumin stability in phosphate buffered saline (PBS), human blood, plasma and culture medium RPMI-1640+10% FBS (pH 7.4, 37^oC). … We conclude that liposomal curcumin may be useful for intravenous administration to improve the bioavailability and efficacy, facilitating in vivo studies that could ultimately lead to clinical application of curcumin.

From Wilken:

Intravenous liposomal curcumin has been studied by our laboratory in mouse xenograft tumors of the oral cancer cell lines CAL27 and UM-SCC-1, and was found to be both nontoxic as well as effective at suppressing tumor growth. Xenograft mouse tumors were stratified into groups receiving no treatment, treatment with empty liposomes or treatment with liposome encapsulated curcumin and a statistically significant growth suppressive effect was observed in the liposomal curcumin group [Wang D, Veena MS, Stevenson K, Tang C, Ho B, Suh JD, Duarte VM, Faull KF, Mehta K, Srivatsan ES, Wang MB: Liposome-encapsulated curcumin suppresses growth of head and neck squamous cell carcinoma in vitro and in xenografts through the inhibition of nuclear factor kappaB by an AKT-independent pathway. Clin Cancer Res 2008, 14:6228-6236.].

From the Abstract (Kurzrock):

Background: Because a role for nuclear factor-.B (NF-.B) has been implicated in the pathogenesis of pancreatic cancer, this transcription factor is a potential target for treatment of this devastating disease. Curcumin (diferuloylmethane) is a phytochemical with potent NF-.B-inhibitory activity. It is pharmacologically safe, but its bioavailability is poor after oral administration.

Methods: We encapsulated curcumin in a liposomal delivery system that would allow intravenous administration. We studied the in vitro and in vivo effects of this compound on proliferation, apoptosis, signaling and angiogenesis using human pancreatic cancer cells.

Conclusions: Liposomal curcumin downregulates the NF-.B machinery, suppresses growth, and induces apoptosis of human pancreatic cells, in vitro. Antitumor and anti-angiogenesis effects are observed in vivo. Our experiments provide a biologic rationale for treatment of patients suffering from pancreatic cancer with this nontoxic phytochemical encapsulated in liposomes for systemic delivery.

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