

DIFFERENTIATING AGENTS

ALL-TRANS-RETINOIC ACID; TRETINOIN; ATRA (VESANOID®)

I. MECHANISM OF ACTION

- A) A derivative of vitamin A, trans-retinoic acid is a differentiating agent and is not specifically cytotoxic or cytostatic.
- B) It is used exclusively to treat acute promyelocytic leukemia (APL), a select form of acute myelogenous leukemia.
- C) In APL, there is a characteristic translocation of genetic material between chromosomes 15 and 17. This results in production of a protein known to suppress normal differentiation of myeloid cells, specifically causing differentiation of neutrophils to cease at the promyelocyte level.
- D) Trans-retinoic acid causes differentiation to continue along its natural course. The exact mechanism by which this occurs is not yet well described.

II. PHARMACOKINETICS

- A) Tretinoin is given orally (10 mg capsules). The absolute bioavailability is not known.
- B) Tretinoin is 96% bound to albumin. It does not cross the blood-brain barrier.
- C) It undergoes extensive metabolism by the cytochrome P-450 system of the liver.
- D) Tretinoin induces its own metabolism resulting in declining plasma concentrations beginning by the seventh day of therapy.
- E) Plasma concentrations may also decline because of an increase in the production of retinoic acid binding protein, which traps the drug intracellularly.
- F) Most of a dose of tretinoin is eliminated in the urine as a metabolite.

III. DOSAGE AND ADMINISTRATION

- A) Tretinoin is given in conjunction with conventional chemotherapy (e.g., idarubicin and cytarabine) in the management of APL.
- B) Dose: 45 mg/m²/day rounded to the nearest 10 mg given in 2 divided doses after food.
- C) Food improves the absorption.
- D) Therapy may continue for 30-90 days.

IV. TOXICITY

- A) Hypervitaminosis A– headache, fever, fatigue, lethargy, cheilitis, arthralgia, bone pain, emesis, pruritus, stomatitis.
- B) Peripheral edema (52%).
- C) Weight gain (23%).
- D) GI complaints are common, such as diarrhea, abdominal pain, dyspepsia, hepatic or splenic enlargement, and elevated LFTs.
- E) Arrhythmias, flushing, and hypertension.
- F) Hypertriglyceridemia.
- G) Retinoic acid syndrome–Most dangerous adverse event. Signs and symptoms include fever, weight gain, respiratory distress, pleural effusions, pulmonary infiltrates, and especially a rapidly rising WBC. At the first signs of RAS, the patient should be started on dexamethasone 10 mg IV q12h for at least 3 days or until resolution of symptoms. Trans-retinoic acid can be continued unless the reaction is absolutely life threatening. Chemotherapy may be given with trans-retinoic acid in order to avoid this reaction, especially if the starting WBC is high (e.g., $> 20 \times 10^9/L$. The exact threshold varies from institution to institution). Occurs in approximately 20% of patients.
- H) Central nervous system reactions include dizziness, confusion, insomnia, increased intracranial pressure, tremor, or encephalopathy.
- I) Teratogenesis.
- J) Otagia and hearing loss.

ARSENIC TRIOXIDE (As₂O₃) (TRISENOX[®])

I. MECHANISM OF ACTION

The mechanism of action of arsenic trioxide is not completely understood. As₂O₃ causes morphological changes and DNA fragmentation characteristic of apoptosis in NB4 human promyelocytic leukemia cells *in vitro*. As₂O₃ also causes damage or degradation of the fusion protein PML-RAR alpha.

II. PHARMACOKINETICS

- A) The metabolism of arsenic trioxide involves reduction of pentavalent arsenic to trivalent arsenic by arsenate reductase and methylation of trivalent arsenic to monomethylarsonic acid and monomethylarsonic acid to dimethylarsinic acid by methyltransferases. The main site of methylation reactions appears to be the liver. Arsenic is stored mainly in the liver, kidney, heart, lung, hair, and nails.
- B) Excretion: disposition of arsenic following IV administration has not been studied. Trivalent arsenic is mostly methylated in humans and excreted in urine.

III. DOSAGE AND ADMINISTRATION

- A) As₂O₃ should be diluted with 100 – 250 mL of 5% glucose or 0.9% NaCl.
- B) As₂O₃ should be administered intravenously over 1 – 2 hours. The duration of infusion can be extended up to 4 hours if acute vasomotor reactions are observed.
- C) As₂O₃ does not need to be infused through a central line.
- D) As₂O₃ ampoules are for single-use and are preservative free. The diluted solutions are stable for 24 hours when stored at room temperature and for 48 hours when refrigerated.
- E) As₂O₃ dosing depends on the phase of treatment. For Induction Therapy, the dose is 0.15mg/kg IV QD until bone marrow remission. The total induction dosage should not exceed 60 doses. The Consolidation Therapy dosage is 0.15mg/kg daily for 25 doses over a period of 5 weeks (i.e. daily from Monday – Friday). Consolidation therapy should start 3 – 6 weeks after completion of induction therapy. NOTE: the recent report by Westervelt et al suggests dosing the As₂O₃ on a maximum of 150% of the ideal body weight in obese patients.
- F) Prior to administering arsenic trioxide a baseline 12-lead EKG should be performed. The QTc interval should be less than 500 msec. Do not start the infusion until this is documented and signed by the physician. Recommended monitoring includes a 12-lead EKG 3 times prior to doses in the first week of therapy, followed by a 12-lead EKG twice a week during treatment. Potassium and magnesium should be within normal limits prior to each infusion of arsenic trioxide. If the patient complains of any "chest fluttering", chest pain, and dizziness – the infusions should be temporarily stopped and a 12-lead EKG performed stat.

IV. TOXICITY

- A) APL differentiation syndrome: several patients treated with As₂O₃ have experienced symptoms similar to the retinoic-acid syndrome. Promyelocytic leukemia or APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. The syndrome can be fatal if not treated immediately. The best treatment is to immediately initiate high-dose corticosteroids (dexamethasone 10mg IV BID) when the WBC count starts to increase or if there is the presence of other signs and symptoms of the syndrome (unexplained fever, dyspnea, weight gain, abnormal chest auscultatory findings or radiographic abnormalities). This has been shown to mitigate signs and symptoms. The steroids should be continued for 3 days or longer, or until signs and symptoms have abated.
- B) EKG abnormalities: As₂O₃ has been shown to prolong the QTc interval. QT prolongation can lead to torsade de pointes-type ventricular arrhythmias. The risk of torsades de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging drugs, a history of torsades de pointes, preexisting QT prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia. In addition, As₂O₃ causes T-wave abnormalities, second-degree heart block, and ventricular arrhythmias. 3 cases of sudden death in the face of no other risk factors has occurred [[Blood 2001;98:266 - 71](#)].
- C) Peripheral sensori-motor neuropathy: with symptoms ranging from paresthesias to paresis has been reported.
- D) Others: skin rashes, musculoskeletal pain, nausea, headaches, dizziness, elevated creatinine and liver transaminases, high-frequency hearing loss, amylase elevations.

V. CLINICAL MONITORING

EKG and electrolyte monitoring prior to starting therapy with As₂O₃, a 12-lead EKG should be performed as well as serum electrolytes, including potassium, calcium and magnesium, and serum creatinine. If the results are outside the normal range they must be corrected prior to the administration of arsenic trioxide. If the patient is taking any medications known to prolong the QTc interval these should be discontinued. If the QTc is > 500 msec, corrective measures should be undertaken, and the QTc reassessed with serial EKG's prior to therapy with As₂O₃. If the QTc interval increases to > 500 msec during therapy with As₂O₃, the patient should be immediately reassessed and immediate action should be taken to correct concomitant risk factors. If syncope, rapid or irregular heartbeat develops, the patient should be hospitalized for monitoring and serum electrolytes. The As₂O₃ should not be reintroduced until the QTc is < 460 msec, electrolyte abnormalities have been corrected, and the syncope and irregular heartbeat ceases.