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COMPRISING THE LONG ISLAND, NEW YORK CITY, RUTH LAWRENCE, UPSTATE NEW YORK, AND WESTERN NEW YORK POISON CENTERS

Vistonuridine®: A Novel Antidote for 5-fluorouracil

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Vistonuridine (PN401 or 2',3,'5'-tri-*O*-acetyluridine) is a newly approved orphan drug that demonstrates promising results as an antidote for 5-fluorouracil (5-FU) overdoses.

Fluorouracil is a pyrimidine antimetabolite frequently used as a part of various chemotherapeutic regimens. It is a fluorinated analogue of uracil, a naturally occurring pyrimidine. 5-FU is a prodrug with two principle cytotoxic metabolites: fluorodeoxyuridine monophosphate **(5-FdUMP)** and fluorouridine triphosphate **(FUTP)** [1-7].

FdUMP exerts its cytotoxic activity via interference with DNA synthesis. It binds to thymidine synthase, the key enzyme required for the production of thymidine, one of the four building constituents of DNA [1-7]. In addition, FdUMP can be converted via a series of enzymatic steps to fluorodeoxyuridine triphosphate (FdUTP), which in turn, gets inserted directly into DNA in place of thymidine, resulting in DNA strands fragmentation. However, the clinical importance of this incorporation on cytotoxic activity of 5-FU is still unclear [1, 3, 4].

FUTP metabolite can incorporate into RNA instead of uridine triphosphate (UTP) causing disruption of processing and function of RNA [1, 3-7].

The cytotoxic metabolites comprise only a small fraction of the 5-FU dose entering the systemic circulation. About 85 % of 5-FU is metabolized to an inactive compound, **dihydro 5-FU**, by the enzyme dihydropyrimidine dehydrogenase (DPD) in the liver and to some extent in extrahepatic tissues [1, 2].

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Program Announcements ••

Ruth A. Lawrence: Monthly conference: every 4 weeks on Thursdays (11am to noon), and every 4 weeks on Tuesdays (10am-11am).

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Vistonuridine®: A Novel Antidote for 5-fluorouracil

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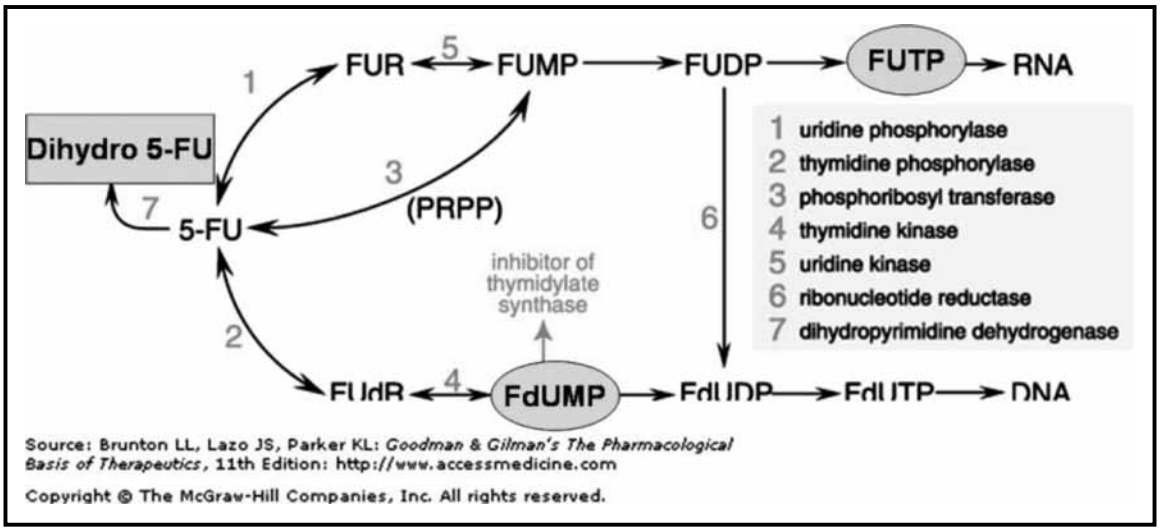
Activation pathway for 5-fluorouracil (5-FU):



(Ref 1)

Fluorouracil is a drug with a narrow therapeutic index. Its clinical usefulness and dosing regimens are limited by severe gastrointestinal and hematological side effects. These unwanted treatment related toxicities are a function of both dose and the rate of administration [8]. Fluorouracil is typically administered as an IV bolus or continuous infusion. Higher total doses can be given via continuous infusion compared with the bolus regimens. The predominating dose limiting toxicities differ depending on the mode of administration [8, 9]. In addition, the untoward reactions are often unpredictable due to their relatively delayed onset and a great interpatient variability in metabolizing capacities of 5-FU. The earliest toxicities typically appear 3 to 8 days after 5-FU administration and include: anorexia, nausea, vomiting, and diarrhea, followed by stomatitis, GI mucosal ulcerations and bleeding. These may lead to dehydration, electrolyte imbalances, enterocolitis progressing to systemic infections, and ultimately sepsis and death[2].

The late toxicities emerge between days 9 to 14, and sometimes as late as after 20 days post 5-FU exposure [2]. These include hematological side effects: myelosuppression, leucopenia, agranulocytosis, and neutropenia, predisposing patients to life threatening infections [2, 3].

A chemotherapeutic regimen is often targeted at the maximum tolerable dose (MTD), with some symptoms of cytotoxicity serving as confirmation of therapeutic efficacy of a chosen pharmacologic agent. Because of nonlinear pharmacokinetics and saturable hepatic clearance of 5-FU, a slight increase in dose or decrease in metabolism of 5-FU can lead to a disproportional increase in a plasma concentration and overall systemic exposure (AUC) [2-5, 7] Thus, unintentional overexposures and overdoses leading to serious toxic reactions are possible during 5-FU treatment [10, 11]. According to the National Institute of Health, about 275,000 patients in the U.S. receive 5-FU every year as a part of their chemotherapy regimen. Approximately 3% of these patients will develop serious treatment related toxicities, and more than 1300 deaths will occur annually due to 5-FU overdoses [11].

Several scenarios can predispose patients to 5-FU overdoses. Excessive amounts of the drug may be given due to dose miscalculations. Infusion pumps, a common mode of 5-FU administration, can predispose patients to overdoses due to errors in programming or due to device malfunctions. In addition, concomitant administration of some chemotherapeutic and non-chemotherapeutic agents may increase 5-FU concentration via drug interactions. For example, leucovorin and methotrexate (frequently co-administered with 5-FU) affect its degradation, increasing chance of toxicities. Genetic abnormalities, such as deficiency in the 5-FU metabolizing enzyme, DPD, can cause serious unpredictable overdoses [3, 4, 11].

Until recently, there was no specific antidote approved for 5-FU overdoses. Patients were managed with supportive care: granulocyte colony-stimulating factors (GCSF), hydration, antiemetics, antibiotics, etc. The possibility of an antidote arose from ongoing research

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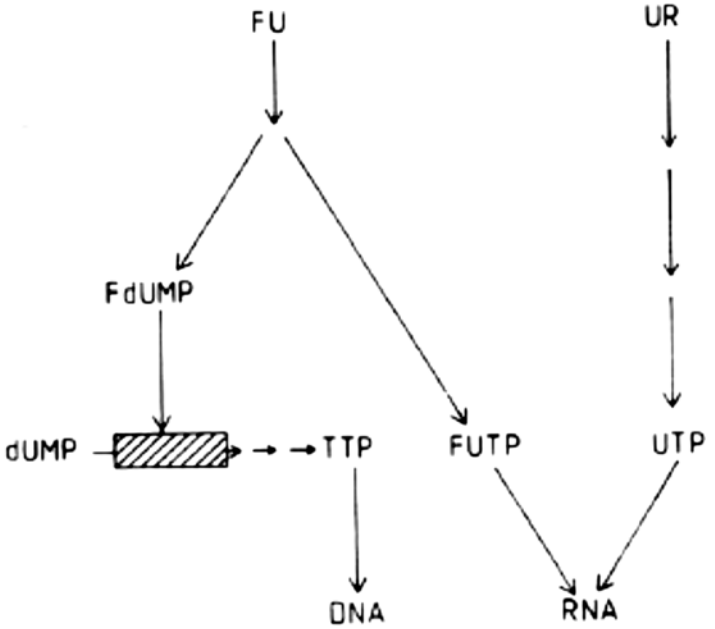
on the biochemical modulation of chemotherapeutic drugs. Biochemical modulators are agents that can augment antitumor activity of a specific chemotherapy drug and/ or decrease its toxicity to normal host tissues via manipulation of the drug's intracellular biochemical pathways [13]. Although a number of chemotherapeutic and nonchemotherapeutic agents have been utilized and experimented with in an attempt to augment antitumor efficacy of 5-FU, only uridine demonstrated promising results as a "rescue" agent in ameliorating 5-FU toxicities [12-14].

Uridine is a naturally occurring pyrimidine nucleoside which competes with 5-FU for incorporation into biochemical pathways. Its utility is based on the evidence that toxicity to rapidly dividing GI mucosa and hematopoietic progenitor cells is primarily mediated via FUTP metabolite interference with RNA transcription and function [5-7, 12-15]. The FdUMP mediated DNA cytotoxic pathway of 5-FU appears to have a less important role in the toxicity of normal tissues [12, 13].



(Ref 13)

Uridine (UR) is converted to uridine triphosphate (UTP) and increases its concentration. UTP then competitively inhibits the incorporation of FUTP metabolite of 5-FU into RNA, limiting unwanted toxicities to normal tissues [5-7, 12-17]. Uridine doesn't interfere with 5-FU antitumor activity when given at least 2 hours post 5-FU administration. However, the optimal time of administration is not clear [12, 14, 15]. The rationale for delayed administration of uridine, as elucidated by Martin et al [12], is that adequate time must be allowed to insure 5-FU elimination from plasma which takes 10-20 minutes. In addition, the initial FUTP incorporation into RNA takes place within 2 hours after administration [12, 14, 15].

The mechanism of selective reduction of 5-FU induced toxicities to normal host cells is not completely understood. However, researchers believe that this selectivity stems from differences in uptake and utilization of uridine between healthy and cancerous cells [7, 12, 13, 18, 19]. It is postulated that rapidly dividing cells of GI mucosa and hematopoietic stem cells can utilize exogenous uridine for biosynthesis of their pyrimidine nucleotides. In contrast, cancerous cells and non-rapidly dividing healthy cells of other tissues prefer de novo pathway for pyrimidine biosynthesis, in which free uridine is not involved [7, 12, 18, 19].

Data obtained from animal and limited human studies demonstrates that delayed administration of parenteral and oral uridine can ameliorate toxicities associated with 5-FU treatment and indirectly improve its antitumor efficacy, allowing for delivery of higher doses of the 5-FU [5,6, 12-16,19]. Clinical effectiveness of uridine, however, was limited by issues with its administration.

Therapeutic serum concentrations of uridine required for protection against 5-FU toxicities is at least 50μmol/L [5, 6]. In contrast, the endogenous concentration in humans is only 3-8 μmol/L [6, 19]. Due to a poor bioavailability (8%), oral uridine doses in the range of 5-12g must be administered to achieve ≥50μmol/L concentration. These large amounts are poorly tolerated, and result in severe nausea and osmotic diarrhea. Parenteral administration of uridine produces complications as well. When given through a peripheral intravenous line, a high incidence of extravasation and phlebitis occur. Administration through a central intravenous line requires meticulous monitoring, and is prohibitively expensive.

An oral prodrug of uridine, Vistonuridine® (PN401 or 2′, 3,′5′-tri-*O*-acetyluridine) was developed by Wellstat Therapeutics Corporation to overcome administration problems with uridine. Because Vistonuridine is more lipophylic than uridine it doesn't require the pyrimidine transporter for absorption across the GI mucosa. As a result, it produces substantially higher systemic uridine concentrations than uridine itself [5, 6]. Once absorption is complete, Vistonuridine is deacetylated by nonspecific esterases to uridine and acetate.

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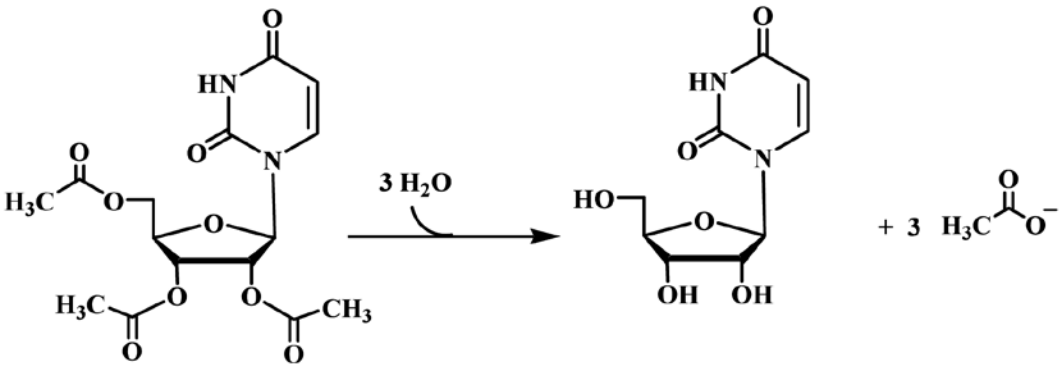

Vistonuridine *Uridine* *Acetate*

Uridine from Vistonuridine is converted to UTP and increases its availability. UTP subsequently competitively inhibits the incorporation of FUTP into RNA, limiting toxicity to healthy tissues in GI mucosa and bone marrow [5-7, 17].

Vistonuridine (PN401) was evaluated in a few preclinical and clinical studies as a "rescue" agent for 5-FU induced toxicities [5-7, 17]. Results of these trials indicate that properly timed administration of Vistonuridine following 5-FU infusion can selectively prevent toxicities to normal host tissues [5-7, 17]. In addition, when added to a 5-FU regimen, Vistonuridine allows dose escalation of 5-FU at least two-fold above typical bolus dose in the range of 500-800 mg/m². As demonstrated by Hidalgo et al, this modest dose augmentation translates into an almost five-fold increase in 5-FU's AUC or systemic exposure, owing to nonlinear pharmacokinetics of 5-FU [5]. This has the potential to improve both 5-FU's toxicity and efficacy profile. Clinical evidence suggests that FdUMP metabolite inhibition of DNA synthesis is a saturable process at the conventional 5-FU bolus doses in the range of 500-600 mg/m². In contrast, FUTP mediated damage to RNA primarily responsible for 5-FU toxicities, may not be saturated at this level of drug exposure. Without biochemical modulation this potentially important mechanism of cytotoxicity may not be taken full advantage of at the standard dose schedules [5, 6, 18].

Different studies with Vistonuridine demonstrate a substantial reduction of 5-FU dose limiting toxicities (DLT): nausea, vomiting, and mucositis [5, 6, 17]. In addition, a study conducted by Doroshow and colleagues demonstrated a substantial reduction of GI toxicities when Vistonuridine was given with the combination of 5-FU and leucovorin. Typically when leucovorin is added to 5-FU-containing regimen, the dose of 5-FU must be reduced to limit a chance of GI toxicities. Vistonuridine enabled a doubling of the usual 5-FU dose and increased the expected duration of survival of patients with advanced gastric cancer [17].

Myelosuppression, predominantly grade 4 neutropenia, became DLT at 1000 mg/m² in study by Kelsen et al and at 1250 mg/m² in study by Hidalgo and colleagues. Discrepancies in maximal tolerated dose between these studies are due to different schedules of Vistonuridine administration. Hidalgo et al demonstrates that the timing of Vistonuridine administration relative to the end of 5-FU infusion is critical for effective attenuation of 5-FU toxicities without interference with its antitumor efficacy [5]. This study evaluates two different schedules for Vistonuridine administration. Vistonuridine was initiated 8 hours post 5-FU infusion and administered at dose of 6 g every 8 hours for 8 doses or every 2 hours for 3 doses, followed by 6 g every 6 hours for 15 doses. Those patients receiving more intensive schedule of Vistonuridine, were able to tolerate higher doses of 5-FU [5, 6,17]. Vistonuridine was well tolerated and did not contribute any additional toxicity to 5-FU containing regimen.

On the basis of these studies Vistonuridine was proposed as a possible antidote for 5-FU overdoses. Vistonuridine was granted orphan drug status by the FDA on May 1st 2009.

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Vistonuridine®: A Novel Antidote for 5-fluorouracil

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Clinical data from 17 patients overdosed with 5-FU and treated with Vistonuridine was presented in June, 2009 at the annual meeting of the American Society of Clinical Oncologists (ASCO) in Orlando, FL. The patients were unintentionally exposed to doses of 5-FU in the range of 3700 to 8000 mg/m² infused for 0.17 -36 hours. All 17 patients treated with Vistonuridine fully recovered [10, 20]. Vistonuridine was employed at doses of 10g every 6 hours beginning 8 to 96 hours after 5-FU overexposure and continued for twenty doses. In agreement with earlier studies, there were no reported toxicities associated with the administration of Vistonuridine at doses employed to manage 5-FU overexposure

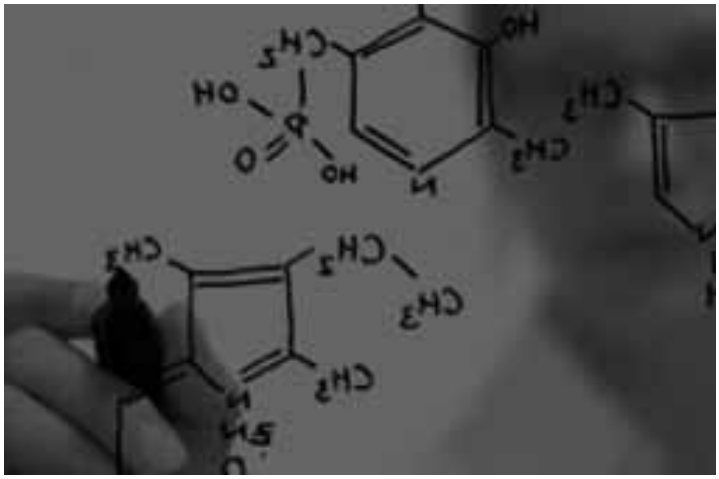
In contrast, historical data obtained from Institute for Safe Medication Practices of Canada was analyzed and used for comparison [20]. Thirteen (13) patients exposed to 3000-10400 mg/m² doses of 5-FU infused over 1-96 hours were managed with the standard treatment of supportive care. Only two patients in this historical cohort survived their overdose.

In conclusion, clinical data presented by Wellstat Therapeutics researchers, as well as the data from earlier studies, demonstrates the effectiveness and safety of Vistonuridine for the management of 5-FU overdoses. However more studies are needed to further determine its optimal dosing schedule and the side effect profile.

Vistonuridine can be obtained directly from Wellstat Therapeutics Corporation upon emergency requests by calling their Safety telephone number:

1-(443)-831-5626

This line is available 24 hours a day, 7 days a week.



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Hydrogen Sulfide: An Agent of Suicide

Contributed by: Jeanna M Marraffa, Pharm.D., DABAT Upstate NY Poison Center, Syracuse, NY

Background:

Hydrogen Sulfide Toxic Gas Production has been increasingly used as an agent of suicide. It was first recognized as a suicidal agent in Japan and the number of deaths in Japan with this method has dramatically risen. Its use has been increasing in the United States and New York.

These cases are being publicized in the media increasing the likelihood of this occurring in your area.

This fact sheet is intended to provide you with some information about this method as well as answers to some commonly asked questions.

What is hydrogen sulfide?

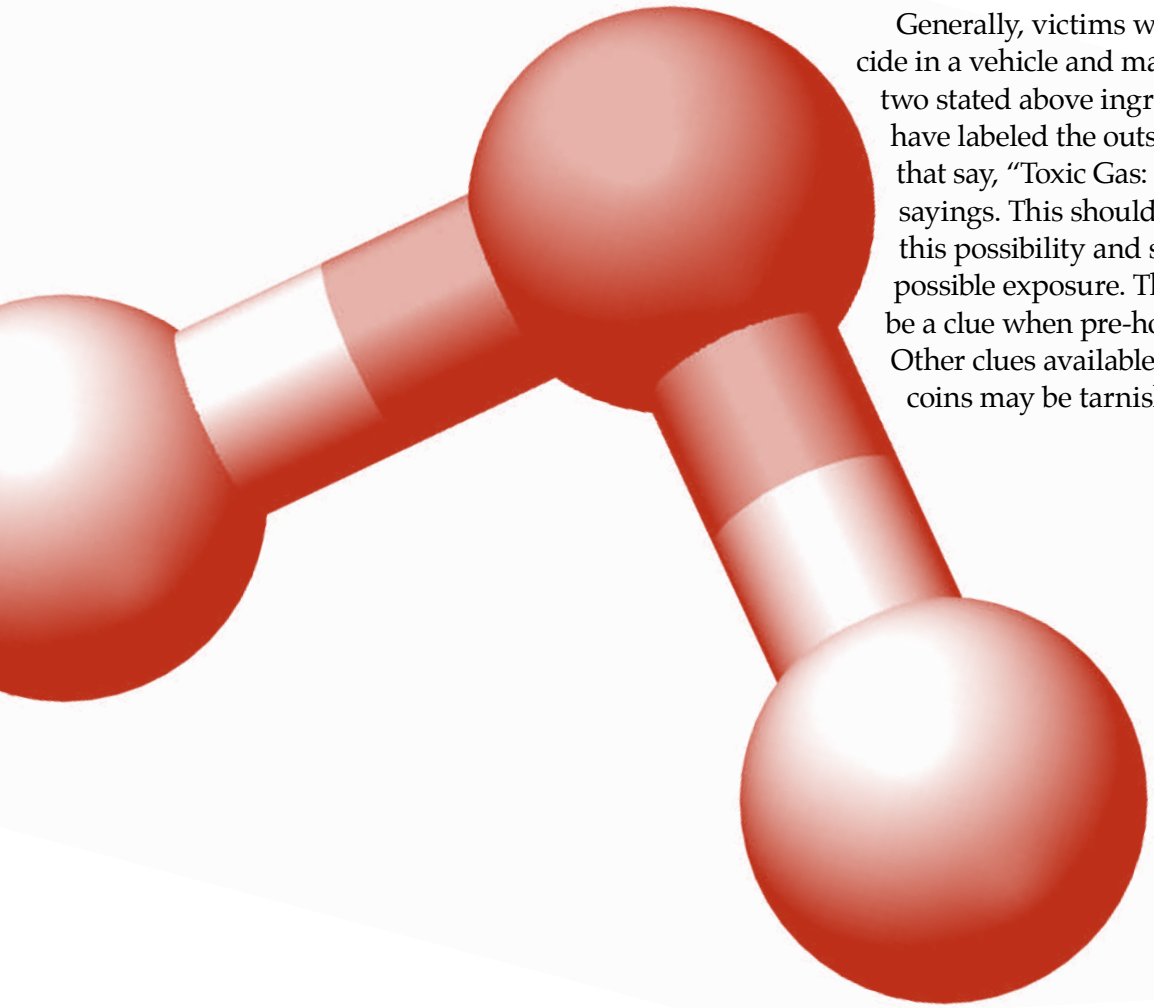
Hydrogen Sulfide (H_2S) is typically thought as sewer gas. It acts similarly to cyanide and inhibits cytochrome oxidase and thereby disrupts the electron transport chain. The end result is a sudden 'knock-down' effect with respiratory and cardiovascular arrest. It is also a pulmonary toxin causing Acute Lung Injury and delayed pulmonary edema after prolonged exposure. Its effects are nearly immediate and removal from the source of exposure often results in improvement of symptoms. Hydrogen Sulfide has a typical smell of 'rotten eggs' because of the sulfur group, however, with increasing concentrations, there is olfactory fatigue. In these cases, the ability to smell H_2S diminishes which may give the victim a false sense of security and therefore, increase the risk of significant toxicity.

How is hydrogen sulfide created as an agent of suicide?

In Japan, H_2S was created by combining sulfur bath with an acid. In the United States, hydrogen sulfide gas is created by the combination of a Sulfur containing pesticide/insecticide + muriatic acid (hydrochloric acid). A commonly used insecticide is Bonide® (which is a 10% Sulfur Spray) plus Muriatic Acid to create Hydrogen Sulfide Gas.

Are there warning signs that hydrogen sulfide is the agent of suicide?

Generally, victims will use this mechanism of suicide in a vehicle and make this gas by combining the two stated above ingredients. Anecdotally, the victims have labeled the outside of their vehicles with signs that say, "Toxic Gas: DO NOT ENTER" or similar sayings. This should alert pre-hospital providers of this possibility and should be a clue that H_2S is a possible exposure. The smell of rotten eggs may also be a clue when pre-hospital providers arrive on scene. Other clues available are that jewelry and penny coins may be tarnished or blackened in color.



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What are the appropriate measures that pre-hospital providers must take?

The pre-hospital providers should be in Level A personal protective equipment (PPE). The car windows should be broken from the furthest point away from the victim.

Once the victim is removed from the car, it is important to remember that the exposure is a gas so skin decontamination is not necessary. Similar to cyanide ingestions, the patients' may be at risk for off-gasing if intubated or if CPR is administered.

What are the treatment modalities for hydrogen sulfide?

Removal from the source is the most important treatment modality for hydrogen sulfide. Appropriate ACLS and supportive care is imperative with obvious attention to Airway, Breathing and Circulation. Patients who remain hemodynamically unstable after removal from the scene and standard resuscitation measures may benefit from sodium nitrite, however the data supporting this is anecdotal and the literature is minimal regarding this.

IMPORTANT KEY POINTS:

- Hydrogen Sulfide is being used as an agent of suicide
- The vehicles are often labeled with "Toxic Gas: Do Not Enter"
- Hydrogen Sulfide is created by the combination of a sulfur containing insecticide/pesiticide (ie: Bonide®) plus muriatic acid (hydrochloric acid)
- First responders must wear Level A PPE
- First responders must enter the vehicle from the furthest point away from the victim
- The victim is exposed to hydrogen sulfide gas; therefore dermal decontamination is not necessary
- The victim may off-gas during CPR and/or endotracheal intubation
- Removal from the Scene and Aggressive ACLS is standard treatment interventions
- Nitrites have been given in refractory patients
- Alert First Responders of this new method of Suicide

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