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Risk Assessment of SilvaSorb Site Dressings on Tracheotomy Insertion Sites and on Renal Transplant Patients, and adult patients in general.

Background: Medline's SilvaSorb Site® dressing is available in two sizes, both of which are suitable for use at the insertion sites of all types of devices. The product was primarily designed for use around Central Venous Catheter (CVC) lines and gastric feeding tubes (G-tubes) and in these functions, the products have served the clinical needs of patients. Thousands of units have been used to date without any reports of adverse events or clinical complaints. SilvaSorb Site has been exhaustively tested for cytotoxicity (on both sensitive fibroblasts and keratinocytes), sensitization, and primary skin irritation. In addition, there is a large body of literature associated with the pharmacological and toxicological properties of silver. Based on laboratory bench and animal studies as well as the safety literature it is expected that there would be no adverse reactions in patients (including neonates) related to the use of the product.

The safety and biocompatibility tests were done to support the submission to the FDA to gain clearance for sales and marketing of the product. The marketing approval was for use on open wounds, which in general by their very nature provide a much bigger portal of entry for the silver ions, than puncture or device insertion sites, into the physiology of critically ill patients. There has been no evidence of toxicological problems in wound healing, though many thousands of units of the SilvaSorb range have been used. SilvaSorb has been effective against all strains of tested microbes, and there is generally no evidence of problematic silver resistance in the general clinical environment.

However, the issue of toxicity of silver on the delicate physiology of critically ill patients needs to be examined in more detail, and the following risk assessment information is relevant to that topic. SilvaSorb Site dressing contains stabilized silver in a reservoir of silver chloride (AgCl) which acts to deliver antimicrobial silver ions, which are released when the silver chloride dissolves in the presence of liquid (e.g. wound fluid or blood, or mucus from mucosal membrane). It is important to remember that silver chloride (AgCl) dissolves in water only until a specific concentration of free ions are achieved. No further dissolution of the silver will occur until those ions are consumed in an independent reaction such as that which occurs when it kill microorganisms. This phenomenon is advantageous as it controls the free silver ion concentration below the level that is toxic for human tissue cells. Thus the concern here is really about the effects of silver ions on the human system, there is no silver metal (ie silver at a zero oxidation state) present in the SilvaSorb Site dressing. Further analysis of toxicological issues is provided below.

Toxicological information on silver:

Acute Toxicity: Acute silver toxicity data in humans have been extrapolated based on animal studies using silver nitrate and silver acetate which are freely soluble silver compounds. No data on the acute toxicity of AgCl (silver chloride) for either systemic or topical application are available perhaps because acute toxic effects from silver chloride,

given the low solubility of the silver salt, has never been observed (and see detailed rationalization below, thus unlikely to be a problem with the SilvaSorb Site product). There is no free silver nitrate in SilvaSorb.

In animal studies, Acute LD 50 (Lethal dose in which 50% of the study population is killed) data are available for silver acetate (23.7 mg silver/kg body weight) and colloidal silver (67 mg/kg body weight) in mice and rats, respectively. Colloidal silver is predominantly silver metal in a zero oxidation state, and the toxicity effects of the colloidal silver, systemically delivered in animals, is not relevant to a discussion around the SilvaSorb Site product that contains no silver metal (only silver ions are present in the product). No intravenous LD 50 values are available for AgCl; The lethal oral dose of greater than 10 g/kg and greater than 5 g/kg determined in mouse and guinea pig, respectively for silver chloride. For all intents and purposes, silver chloride is a non toxic substance.

Chronic Toxicity: The low frequency of the chronic toxicity observed in humans and the high concentrations needed to provoke chronic effects in animals (chronic toxicity in rats were seen in ranges from 1.5 mg silver /kg bw/day, i.v, no toxicity observed at 0.31 mg silver/kg/day body weight (bw) for 30 days) and humans (data suggests a total dose of minimum 1 gm silver per average person, i.e approx 13.3 mg silver /kg bw, assuming avg. body weight at 75 kg, is required to induce chronic toxicity in humans) suggest that rather high doses of silver, administered over many days, is required to cause chronic silver related toxicity.

Discussion:

Considering the low solubility of AgCl (1.93 mg/liter) in aqueous fluids and also its low concentration in the SilvaSorb Site dressing (0.49 mg only in a one inch diameter site dressing), an extrapolation can be made of the animal data that suggests that for acute toxicity to be seen in an average person , one would require at least 2-3 gm of silver in the free ionic state (such as in silver nitrate but not in silver chloride) (from the 23.7 mg/kg bw LD 50 value in animals). Using such extrapolation, the rationale is that the silver ions from about 5000 dressings would have to enter a person at once to show any degree of acute toxicity. Thus, the occurrence of acute intoxication related to the appropriate use of SilvaSorb Site dressing is not to be expected. In addition, it has to be emphasized that the active silver ions are liberated by equilibrium dynamics from SilvaSorb Site dressing (see below) and such equilibrium is only reached slowly, AgCl is a difficultly soluble silver salt. Thus in reality the silver from a theoretical 5000 dressings would not be immediately releasable to elicit its acute toxic effects even under that theoretical 5000 dressing use scenario.

Nevertheless, further quantitative risk assessment associated with the use of the SilvaSorb Site dressing is an appropriate exercise in the context of chronic toxicity potential.

A SilvaSorb Site, one inch diameter dressing, has a total reservoir of 0.369 mg of silver (corresponding to 0.491 mg of silver chloride). Again, similar to the arguments above,

most of the silver is in the form of weakly soluble (and thus inactive) silver chloride, but some of it is present as free silver ions which are responsible for the antimicrobial efficacy and any potential toxicity of the product. One needs to examine the scenario where this low amount of silver somehow finds its way into the delicate physiology of a renal transplant patient and/or a patient with a tracheotomy to elicit chronic toxicity effects..

Given that the solubility of silver chloride is only 1.93 mg/liter, the 0.491 mg of silver chloride present in a one inch SilvaSorb Site dressing would require 254 ml of body fluids (mucus/blood/serum) to dissolve, it is difficult to imagine a clinical scenario in which such a large amount of body fluid comes out of an insertion site or a puncture site to react with the site dressing and dissolve the silver chloride to create the active silver ions. Such dissolution, in this remotely possible scenario, would also be very slow given that slow equilibrium dynamics are involved in such a process. Even more unrealistic is the scenario of this level of fluid (254 ml) re-entering the blood stream after dissolving all the silver in a SilvaSorb Site dressing outside the body. In the scenario where both these unrealistic events were to occur, and there indeed was a case of “silver dumping” and all of the 0.491 mg of silver chloride (corresponding to 0.369 mg of silver) found its way into the blood stream in one catastrophic event, the body concentration in a 75 kg adult would reach only 0.00065 mg/kg bw of silver chloride, or 0.00049 mg/kg bw of silver. These levels, in the context of the above toxicological background information (chronic toxicity at 13.3 mg of silver/kg)on silver and silver compounds are considered to be quite safe and the margin of safety is so large (approx. 2700) that there should be little concern around the toxicological systemic effects of silver, on both the tracheostomy patient and the renal transplant patient, or in general on any adult. Even on infants with a low body weight, the margin of safety is still substantial, providing a rationale for the use of the SilvaSorb Site product on the pediatric population.

Again, the emphasis has to be on the fact that silver dumping through the complete dissolution of the silver chloride in a site dressing by exposure to 254 ml of wound fluid, and the subsequent ingress of that fluid into the average person’s body through the puncture site is a very unrealistic scenario. **And the comforting fact is that even if such unrealistic events were to happen, the concentration of silver in the average adults body would be way below the levels that cause acute and/or chronic toxicity. In addition, there is a great deal of evidence that silver ions are gradually excreted and do not accumulate irreversibly.**

This document examines the toxicological issues only around the use of the SilvaSorb Site product. It has to be borne in mind that studies have shown that the levels of silver ions that are released from SilvaSorb Site are perfectly adequate to control local bioburden around a puncture or insertion site. These studies are available else where. What those studies and the above toxicological discourse proves is that silver ions are able to control local bioburdens at concentrations that are not toxic.

Finally, the tracheostomy and renal transplant patients do not present a challenge any different to the toxicological issues discussed above. The tracheostomy patient would have little chance of coming into contact with thousands of dressings over the course of treatment, and absorb silver from each dressing by ingestion of 254 ml of silver ion saturated mucus from every puncture site. A similar argument of course also applies to the renal patient. Silver ions are excreted both via the gastric system as well as the urinary system, and extremely low levels of silver ions are unlikely to present a problem to the renal system.

SilvaSorb products have been used to treat vaginal and buccal cavity wounds with no adverse effects, which only increases the confidence level that the SilvaSorb product range is safe around body cavities, and puncture wounds.

Conclusion: A risk assessment exercise on the SilvaSorb Site dressing on renal transplant and tracheostomy patients, and on adult patients in general, show that there is little toxicological risk in using the product.