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# Intercoat Gel (Oxiplex): Efficacy, Safety, and Tissue Response in a Laparoscopic Mouse Model

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**ABSTRACT** **Study Objective:** To study the efficacy and safety of Intercoat gel in a laparoscopic mouse model with pneumoperitoneum-enhanced adhesion formation.

**Design:** Randomized controlled trial. Evidence obtained from a properly designed, randomized, controlled trial (Canadian Task Force classification I).

**Setting:** University laboratory research center.

**Subjects:** Balb\c female mice 9 to 10 weeks old.

**Interventions:** Two laparoscopic mouse models for adhesion formation were used. In the first model, adhesions following bipolar opposing lesions in the pelvis were enhanced by 60 minutes of carbon-dioxide pneumoperitoneum. In the second model, adhesions were further enhanced by bowel manipulation. The first experiment evaluated the efficacy of Intercoat in both models. The second experiment evaluated the efficacy of Intercoat in the first model, when applied immediately on the lesion, when applied at the end of the pneumoperitoneum, and when applied in the upper abdomen. Biopsy specimens were taken after 7 days and were evaluated after hematoxylin-eosin and CD45 staining.

**Measurements and Main Results:** Qualitative and quantitative adhesion scoring. Morphology was evaluated by standard light microscopy. In both models, Intercoat decreased adhesion formation whether applied immediately on the lesion or at the end of the pneumoperitoneum (qualitative and quantitative scoring $p < .0001$ and $p < .0001$, respectively). Intercoat application is associated with tissue redness, vascular congestion, and cellular edema but without an inflammatory reaction. Applied in the upper abdomen, Intercoat does not increase adhesions, but decreases adhesions at higher doses ($p = .0024$). Intercoat in high doses had a toxic effect ($p = .0058$).

**Conclusion:** Intercoat is an effective antiadhesion product. It is associated with tissue edema and vasodilatation as observed after 7 days both macroscopically and by histology. Journal of Minimally Invasive Gynecology (2009) 16, 188–194 © 2009 AAGL. All rights reserved.

*Keywords:* Adhesion formation; Intercoat; Oxiplex; Laparoscopy; Animal Model

Barriers are widely used for adhesion prevention, because adhesion formation has been viewed as a local process of slow or incomplete fibrin degradation at the trauma site permitting fibroblast proliferation instead of mesothelial repair. Separation of peritoneal surfaces until mesothelization has occurred may prevent or lessen adhesion formation. The barriers can be nonresorbable solid membranes, resorbable solid membranes, or resorbable semisolid gels. Although efficacy of nonresorbable solid membranes was elegantly proved [1], they never became popular because a second intervention was necessary to remove them. All resorbable barriers today are based on carbohydrate polymers such as hyaluronic acid, carboxymethylcellulose (CMC), polyethylene glycol (PEO), oxidized regenerated cellulose, and polytetrafluoroethylene. Combination of products and degree of chemical cross-linking will result in solid membranes or gels.

Solid barriers such as Seprafilm (Genzyme, Cambridge, MA), containing hyaluronic acid-CMC, and Interceed (Johnson & Johnson, Gynecare Unit, Somerville, NJ), oxidized

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regenerated cellulose reduced adhesion formation by some 50% in animal models and in human beings [2–8]. They can be used adequately only in laparotomy. Semisolid gels such as SprayGel (Confluent Surgical, Waltham, MA), using PEO, and Hyalobarrier Gel (Baxter, Pisa, Italy), using auto-cross-linked hyaluronic acid, seem to be equally effective and safe. Moreover, they can be used easily during laparoscopic surgery [9–21]. Developed as a local adhesion prevention barrier applicable at laparoscopy, Intercoat/Oxiplex/SP Gel is composed of PEO and CMC. Manufactured as a thin sheet, it was proved to be effective in a rabbit laparoscopy model [22], and in the human being it reduced epidural fibrosis and radiculopathy after lumbar surgery [23,24]. A gel preparation reduced adhesion formation after laparoscopic adnexal surgery [25] in nonendometriosis and in endometriosis surgery [26]. These resorbable solid or semisolid barriers appear to be safe, with few side effects, which is not surprising because they are based on natural products. Efficacy is comparable, which also is not surprising because they are chemically related. The pathophysiology of adhesion formation, however, is surprisingly poorly documented.

During the last decade, injury to the mesothelial cells of the peritoneal cavity was revealed as a cofactor in adhesion formation at the injury site [27]. This was shown for carbon-dioxide ($CO_2$) pneumoperitoneum, which increases adhesion formation as a time- and pressure-related effect [28]. Scanning electron microscopy showed that mesothelial cells retract with direct exposure of the extracellular membrane. It was postulated to be mediated through mesothelial hypoxia because it was prevented by adding low doses of oxygen to the pneumoperitoneum [29] and absent in HIF1a and HIF2a knockout mice and because it was decreased by drugs preventing hypoxia-inducible factor induction [30]. Also, desiccation enhances adhesion formation [31] as does mechanical manipulation of the bowel in the upper abdomen.

The mechanism of action of any product used for adhesion prevention could thus be local at the trauma site, e.g., by keeping the surfaces separated until reepithelialization, or through the peritoneal cavity by preventing or reducing mesothelial trauma or by preventing deleterious effects from the peritoneal cavity to reach the traumatized area. This prompted us to evaluate the last developed product, Intercoat in our laparoscopic mouse model.

## Materials and Methods

### *The Laparoscopic Mouse Model for Adhesion Formation*

The experimental setup (i.e., animals, anesthesia and ventilation, laparoscopic surgery, and induction and scoring of intraperitoneal [IP] adhesions) was described in detail previously [27–30,32–34]. Briefly, the model consisted of pneumoperitoneum-enhanced adhesions induced by a mechanical lesion. The pneumoperitoneum was maintained for 60 minutes using pure and humidified $CO_2$ at 15 mm Hg of insufflation pressure. Gas and body temperatures were kept strictly at 37°C using a heated chamber. Female Balb/c mice, 9 to 10 weeks old and weighing 19 to 24 g, were used because adhesion formation is high whereas the interanimal variability is low in this inbred strain [35]. Animals were kept under standard laboratory conditions and they were fed with a standard laboratory diet with free access to food and water. The study was approved by the institutional review animal care committee.

Mice were anesthetized with IP 0.08 mg/g of pentobarbital, intubated with a 20-gauge catheter, and mechanically ventilated (Mouse Ventilator MiniVent, type 845, Hugo Sachs Elektronik-Harvard Apparatus GmbH, March-Hugstetten, Germany) using humidified room air with a tidal volume of 250 μL at 160 strokes/min to prevent cooling.

A midline incision was performed caudal to the xyphoid, a 2-mm endoscope with a 3.3-mm external sheath for insufflation (Karl Storz, Tüttlingen, Germany) was introduced into the abdominal cavity, and the incision was closed gas tight around the endoscope to avoid leakage. The pneumoperitoneum was created with the Thermoflator Plus (Karl Storz) using humidified insufflation gas [31,36]. After the establishment of the pneumoperitoneum, 2 14-gauge catheters were inserted under laparoscopic vision. Standardized 10- by 1.6-mm lesions were performed in the antimesenteric border of both right and left uterine horns and pelvic sidewalls with bipolar coagulation (BICAP, bipolar hemostasis probe, BP-5200A, 5 Fr, 200 cm; IMMED Benelux, Linkebeek, Belgium) at 20 W (standard coagulation mode, Autocon 200, Karl Storz).

Adhesions were scored qualitatively and quantitatively under microscopic vision by a blinded investigator during laparotomy 7 days later. Indeed, scoring after 7 and 28 days was proved previously not to be different [27], whereas scoring after 7 days is much more convenient for planning of experiments. The qualitative scoring system assessed extent (0: no adhesions; 1: 1%–25%; 2: 26%–50%; 3: 51%–75%; 4: 76%–100% of the injured surface involved), type (0: no adhesions; 1: filmy; 2: dense; 3: capillaries present), and tenacity (0: no adhesions; 1: easily fall apart; 2: require traction; 3: require sharp dissection) of adhesions, from which a total score was calculated (extent, type, tenacity). The quantitative scoring system assessed the proportion of the lesions covered by adhesions using the following formula: adhesion (%) = (sum of the length of the individual attachments/length of the lesion) × 100. The results are presented as the average of the adhesions formed at the 4 sites (right and left visceral and parietal peritoneum), which were individually scored.

To control temperature, animals and equipment (i.e., insufflator, humidifier, water valve, ventilator, and tubing) were placed in a closed chamber maintained at 37°C (heated air, WarmTouch, Patient Warming System, model 5700, Mallinckrodt Medical, Hazelwood, MO). The insufflation gas temperature was determined by the environmental temperature, i.e., at 37°C. Because anesthesia and ventilation can influence body temperature and body temperature can influence adhesion formation [31], the timing and

temperature were strictly controlled. Mouse temperature was measured by rectal probe before anesthesia and was between 35°C and 37.7°C for all mice. The time of the anesthesia injection was considered time 0. The animal preparation and ventilation started after exactly 10 minutes. The pneumoperitoneum started at 20 minutes and was maintained for 60 minutes for a total time of 80 minutes.

Two models of adhesion formation were used to mimic the clinical situation. The first model consisted of adhesion formation following opposing bipolar lesions and 60 minutes of pure $CO_2$ pneumoperitoneum ($CO_2$ pneumoperitoneum/hypoxia-enhanced adhesions). In the second model, these $CO_2$ pneumoperitoneum-enhanced adhesions were further enhanced by 5 minutes of manipulation of omentum and bowels in the upper abdomen (hypoxia- and manipulation-enhanced model). These models mimic the clinical situation of a peritoneal lesion together with the effect of $CO_2$ pneumoperitoneum (model 1), further enhanced by surgical manipulation (model 2).

### *Design of the Experiments*

Intercoat, a viscoelastic gel composed of polyethylene oxide and carbomethylcellulose was received from Ethicon Inc (FzioMed, Ethicon, Somerville, NJ). Intercoat was administered with a sterile syringe and a 14-gauge catheter.

Experiment I (n = 24) was performed to evaluate the efficacy of Intercoat gel on adhesion formation in model 1 (hypoxia-enhanced adhesion formation) and in model 2 (hypoxia- and manipulation-enhanced model) and to evaluate whether efficacy was similar in both models. A factorial design with 6 animals in each of the 4 groups was used, i.e., $CO_2$ pneumoperitoneum-enhanced adhesions without and with manipulation, each of them without and with Intercoat application (0.7 mL of Intercoat applied on the lesions immediately after the lesion was made for model 1 or immediately after manipulation for model 2). Animals were block randomized by day, i.e., 1 animal of each group was operated on the same day in random order.

Experiment II (n = 49, 7 animals/group) was designed to answer 2 questions. First, is the effect of Intercoat caused by the barrier effect between the opposing lesions only, or does Intercoat in addition attenuate the effect of hypoxia by shielding the lesion from the hypoxic effect of $CO_2$? Second, we wanted to exclude that the inflammatory/edematous reaction observed in the first experiment might contribute to adhesion formation, thus Intercoat having possibly a dual effect, a barrier effect reducing adhesions and an inflammatory reaction possibly enhancing adhesions. To answer the first question, 0.7 mL of Intercoat was applied on the lesions immediately after the lesions were made (group II) or at the end of pneumoperitoneum (group III) in comparison with a control group (group I). To answer the second question, 0.2, 0.5, and 1 mL of Intercoat were administered in the upper abdomen after induction of the lesions (group V, VI, and VII, respectively). In addition, in group IV, 0.7 mL of Intercoat was administered on the lesions together with 1 mL in the upper abdomen. Animals were block randomized by day, i.e., 1 animal of each group was performed in 1 day, but in random order.

To evaluate tissue reaction to Intercoat, biopsy specimens were taken from the omentum. The biopsy specimens were embedded with JB solution (Canemco, Quebec, Canada) and fixed in paraffin. Control samples were stained with hematoxylin-eosin. Samples from the treated mice were stained with hematoxylin-eosin and immunohistochemistry staining for CD45 with purified rat antimouse CD45, in a 3-step staining procedure with combination with biotin-conjugated rabbit antirat as the secondary antibody and streptavidin together with diaminobenzidine as a detection system. Because we looked for inflammatory reaction, we used anti-CD45, because CD45 is found on all cells of hematopoietic origin except erythrocytes. Its presence distinguishes leukocytes from nonhematopoietic cells.

### *Statistics*

Statistical analyses were performed with the software (SAS System, SAS Institute, Cary, NC) using for the first experiment a 2-way analysis of variance (general linear methods, proc GLM) with manipulation and Intercoat as variables. In the second experiment, differences in adhesion proportions between 2 groups were evaluated by Wilcoxon test (Graph Pad Software Inc, San Diego, CA). Correlation between postoperative mortality and total amount of Intercoat administration was checked with Spearman correlation.

Power analysis was based on the low interanimal variability in inbred Balb\c mice (<5%). The first experiment had a power of 90% to detect a difference of 7% for each factor because the factorial design with a 2 analysis of variance has almost the same power for each variable as if the experiment were conducted sequentially for each variable with 12 animals in each group [28]. The second experiment had a power of 90% to detect a difference of 10% between groups.

## Results

The first experiment confirmed the increase in adhesion formation by manipulation and the decrease by Intercoat. Adhesion reduction was found whether evaluated as quantitative adhesion proportions ($p < .0001$) (Fig. 1) or as a qualitative scoring of adhesion formation, i.e., total adhesion score, extension, type, or tenacity ($p < .0001$, $p < .0001$, $p = .0002$, and $p = .0002$, respectively, proc GLM). The reduction, moreover, was not specific for manipulation-enhanced adhesions, because the percent reduction in adhesions was similar in both models, i.e., with and without manipulation.

In experiment II Intercoat similarly reduced adhesion formation whether applied immediately after induction of the lesion or at the end of pneumoperitoneum ($p = .097$ and $p = .0051$, respectively, Wilcoxon test) (Fig. 2). Intercoat applied in the upper abdomen did not increase adhesion

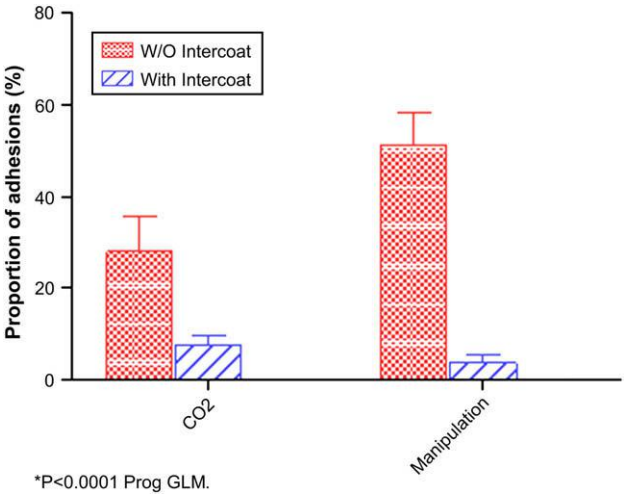


Fig. 1. Reduction of adhesion formation (quantitative scoring) by Intercoat in 2 laparoscopic mouse models. In the first model, adhesions following coagulation lesions were enhanced by 60 minutes of $CO_2$ pneumoperitoneum. In second model, adhesions were further enhanced by bowel manipulation. W/O = Without.

formation; to the contrary, a decrease in adhesion proportion was found with higher doses. This reduction was observed for the quantitative scoring (0.2 mL vs 0.5 mL and 1 mL; p =.0177 and p =.0024, respectively, Wilcoxon test) and for the qualitative adhesion score, i.e., total score, extension, type, and tenacity (p =.0113, p =.0024, p =.0338, and p =.0278, respectively, proc GLM).

Intercoat in higher doses was associated with increased mortality in mice (p =.0058, Spearman correlation) being 85.7% when 1.7 mL was used (1 mL in the upper abdomen and 0.7 on the lesion) versus 28.5%, 28.5%, and 0% when 1, 0.5, and 0.2 mL were used in the upper abdomen, respectively, and 14.2% after 0.7 mL on the pelvic lesions. In total, 12 mice died between 4 and 7 days postoperatively.

Intercoat application in mice was associated on day 7 with ascites and hyperemia. To evaluate whether this macroscopic observation of hyperemia was caused by inflammation, biopsy specimens were taken in group 7 (1 mL of Intercoat), i.e., the highest dose of Intercoat used. Because 85.7% of the mice in group 4 (0.7 mL on the lesion and 1 mL at the upper abdomen of Intercoat) died, this group could not be used. The histology showed in the Intercoat-treated mice important capillary dilation, hyperemia, and cellular edema of the connective tissue cells, which were absent in the control samples (Fig. 3). Immunohistochemistry staining with CD45 that stain leukocytes and lymphocytes did not show marked inflammatory response in this tissue.

## Discussion

Intercoat was confirmed to effectively decrease adhesion formation in both the laparoscopic mouse models, i.e., with $CO_2$ pneumoperitoneum-enhanced adhesions and in the model of $CO_2$- and manipulation-enhanced adhesions (Fig. 1). The effect is proportional to the adhesions and is not specific for either $CO_2$-enhanced adhesions or manipulation-enhanced adhesions. These results confirm and extend the 91% reduction in adhesions by a similar CMC and PEO film [22] in rabbits and rats. Our results also confirm and extend the previous indication of efficacy of barriers such as SprayGel (Confluent Surgical) and Hyalobarrier Gel (Baxter) in the pneumoperitoneum-enhanced laparoscopic adhesion model.

Because the effect of Intercoat application on the lesion is similar whether applied immediately after injury or at the end of the pneumoperitoneum, we suggest that the direct effect of the $CO_2$ pneumoperitoneum on the lesion area is limited. This is compatible with the hypothesis that the effect is transmitted by factors released from the entire peritoneal cavity after hypoxic injury. The pathophysiology of the antiadhesive effect of Intercoat is believed to be a consequence of its barrier effect keeping the injured surfaces separated for sufficient time [25]. It remains possible, however, that in addition these barriers are also effective by preventing the deleterious effects from the peritoneal cavity to reach the injured areas, e.g., those induced by hypoxia, reactive oxygen

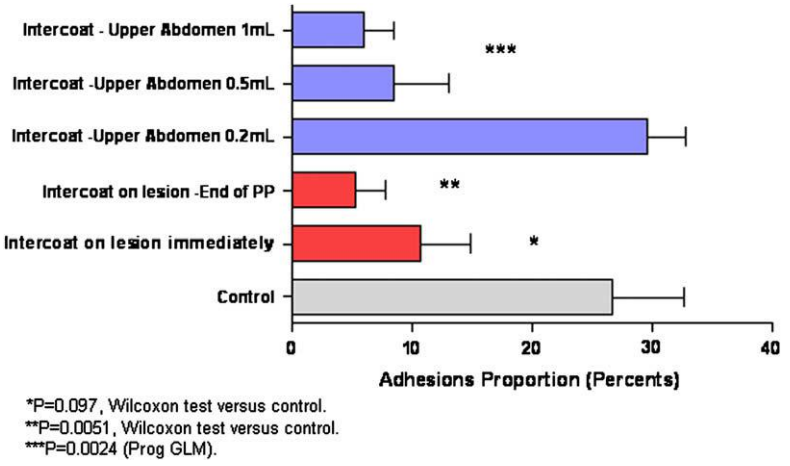


Fig. 2. Effect of Intercoat on adhesion formation when applied on lesion at beginning or end of pneumoperitoneum (PP) and when applied in upper abdomen.

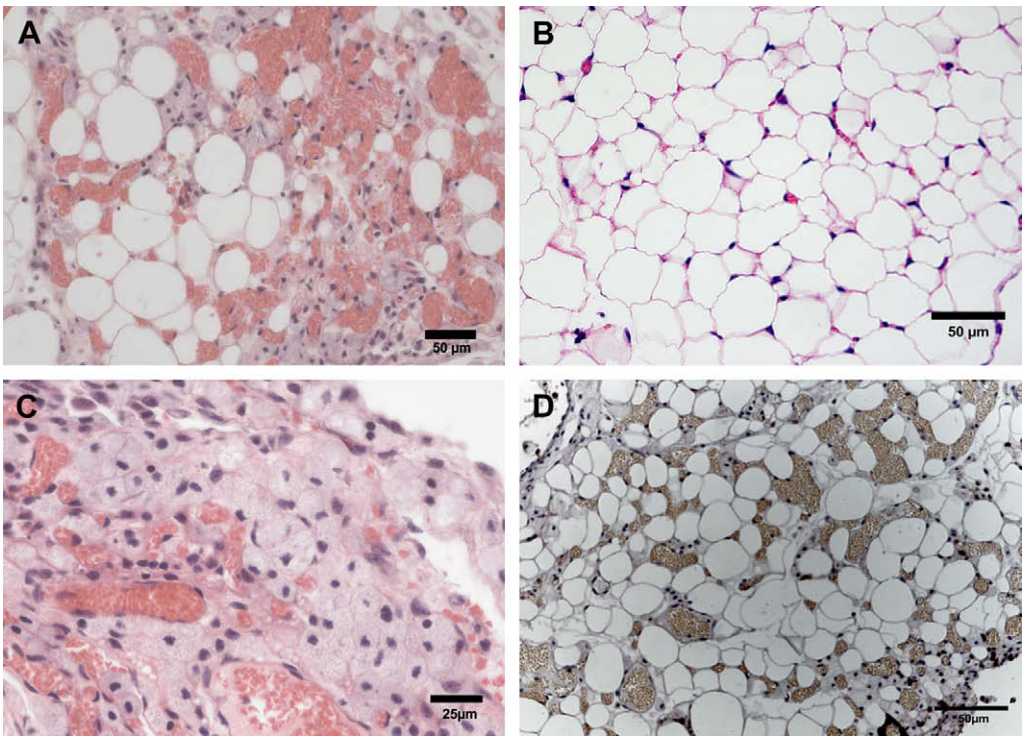


Fig. 3. Histologic biopsy specimens from Intercoat-treated mouse showing omentum with severe capillary dilation (**A**) in comparison with control omentum biopsy specimens (**B**) and edema of connective tissue cells (**C**). CD45 staining does not show inflammatory cells (**D**).

species, desiccation, and manipulation. In addition, any semiliquid product could spread over the entire peritoneal cavity and thus affect any deleterious influence from the peritoneal cavity on adhesion formation at the injured areas. The experiments with application in the upper abdomen clearly show a dose-dependent antiadhesiogenic effect. Because 0.2 mL in the upper abdomen is less effective, we suggest that the effectiveness of the upper abdomen application of 0.5 and 1 mL is a consequence of spreading of the gel after surgery by bowel and body movements.

Intercoat is a gel containing CMC and PEO (i.e., a polysaccharide and a polyether, respectively). The added calcium chloride creates an ion complex with PEO, determining rheology, tissue adherence, and resistance time [37]. Carboxymethylcellulose is tissue adhesive, thus acting as a local barrier. The PEO has a high viscosity thus contributing to the barrier effect. However, PEO also has a high osmotic pressure thus increasing peritoneal fluid and tissue edema with hyperemia. Leukocyte concentrations are reduced in the peritoneal fluid after IP PEO treatment, but it is unclear whether this is a mere dilution effect [38]. This osmotic effect might also affect adhesion formation. Indeed, the osmotic effect is associated at least with a dilution of all factors in the peritoneal fluid whether increasing or decreasing adhesion formation. The tissue edema and hyperemia could affect tissue healing. This effect might also be responsible for the high mortality when used in high doses in small animals such as mice. In any case, none of the studies on Intercoat revealed toxicity effect when given IP [25,26]. In this experiment the doses used in mice in comparison with the animals' weight were much higher compared with the use in human beings but were necessary to have sufficient coverage of the lesion.

The overall efficacy of Intercoat might thus be a consequence of the local barrier effect of preventing deleterious substances from the peritoneal cavity to reach the injured area and by the osmotic effect. Our experiments unfortunately do not permit quantitative differentiation between these effects. First, mice are very small animals with obvious spreading of the Intercoat over the peritoneal cavity. Second, with Intercoat in our model being more than 80% effective, it becomes difficult to show additive effects from the 3 different potential mechanisms.

During both experiments we observed, during adhesion scoring after 1 week, that mice treated with Intercoat had marked redness of the peritoneal cavity and increased IP fluid. This, to our knowledge, was not reported before. This observation was confirmed by histology showing edema and capillary dilatation (Fig. 3). Fortunately, we did not find signs of inflammation whereas application of Intercoat in the upper abdomen did not increase adhesion formation. We, therefore, conclude that Intercoat does not cause inflammation of the peritoneal cavity. We consider this very important because Intercoat could have a double effect, i.e., decreasing the adhesions through a local barrier effect while increasing adhesions through peritoneal cavity irritation.

Redness and increased peritoneal fluid 1 week after Intercoat application was not reported before, nor was

dose-dependent mortality in mice. Both could be considered a reason for concern. This redness was shown to be a consequence of local hyperemia and cellular edema but without inflammatory reaction (Fig. 3). The increased IP fluid probably is also related to this osmotic effect. It is unknown, although likely, whether a similar effect exists for other barriers. The high mortality in mice after the application of higher doses is suggested to be a consequence of this osmotic effect and dehydration. In any case, none of the studies on Intercoat indicated toxicity effect when given IP in human beings [25,26]. The doses necessary in small animals such as mice to cover the lesion indeed are relatively much higher than in larger animals and in human beings. Whether this local edema should be a cause of concern when applied over bowel lesions or bowel sutures remains unknown.

In conclusion, Intercoat is proved to be an effective antiadhesion product in our model. It probably acts as a local barrier at the level of the lesions, but it cannot be excluded that it also reduces the deleterious effect of the peritoneal cavity on adhesion formation. Moreover, Intercoat causes vascular congestion and intracellular edema, probably because of high osmotic effect of its components, an effect that also might influence adhesion formation. Mice unfortunately are animals too small to differentiate between these effects. The mortality with high doses is believed to be a consequence of the osmotic effect and should not be a concern in the human being. Because all antiadhesive barriers today are based on carbohydrate polymers, similar tissue effects can be expected.

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