

# Necrosis of a guinea pig stomach after contact with povidone-iodine: a case report

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## Abstract

Rodents are the most frequently used animals in surgical experimentation. It is estimated that guinea pigs in particular are the third most commonly used species in this context. To disinfect guinea pigs' skin, either alcohol or surgical iodine are most often used. In the context of an animal research project, a Nissen operation was performed in an adult male guinea pig. Because of accidental contamination of the operative field, a 10% povidone-iodine cutaneous solution was applied to the serosa of the anterior wall of the stomach and to the gastric fundus. The guinea pig died 12 hours after surgery due to an acute necrotizing hemorrhagic gastritis. Although there have been a few reports of povidone-iodine toxicity in the guinea pig, as far as the authors could determine, this is the first time that such a serious abdominal complication is reported. The authors believe that the possibility of a similar event should be taken into consideration when planning, executing and interpreting experiments in the guinea pig.

**Keywords:** refinement, guinea-pig, povidone-iodine, toxicity, animal experiment.

## 1 Introduction

Rodents are the most frequently used animals in surgical experimentation (GREEN, 1987; TAMAI, 2004; BEYNEN and HAU, 2006; PAPADIMITRIOU, XANTHOS, DONTAS et al., 2008; BARAN, PERRET-GENTIL, JOHNSON et al., 2011). It is estimated that guinea pigs in particular are the third most commonly used species in this context (CUNLIFFE-BEAMER, 1993). It has been clearly demonstrated that aseptic technique is of paramount importance in avoiding post-surgical infection, which minimizes experimental animals' morbidity and mortality, and eliminates a source of uncontrolled variation in research data (BRADFIELD, SCHACHTMAN, MCLAUGHLIN et al., 1992; BROWN, PEARSON and TOMSON, 1993; CUNLIFFE-BEAMER, 1993; COUNCIL, 1996; HUERKAMP, 2002; BAUMANS, REMIE, HACKBARTH et al., 2006; RUTALA and WEBER, 2008).

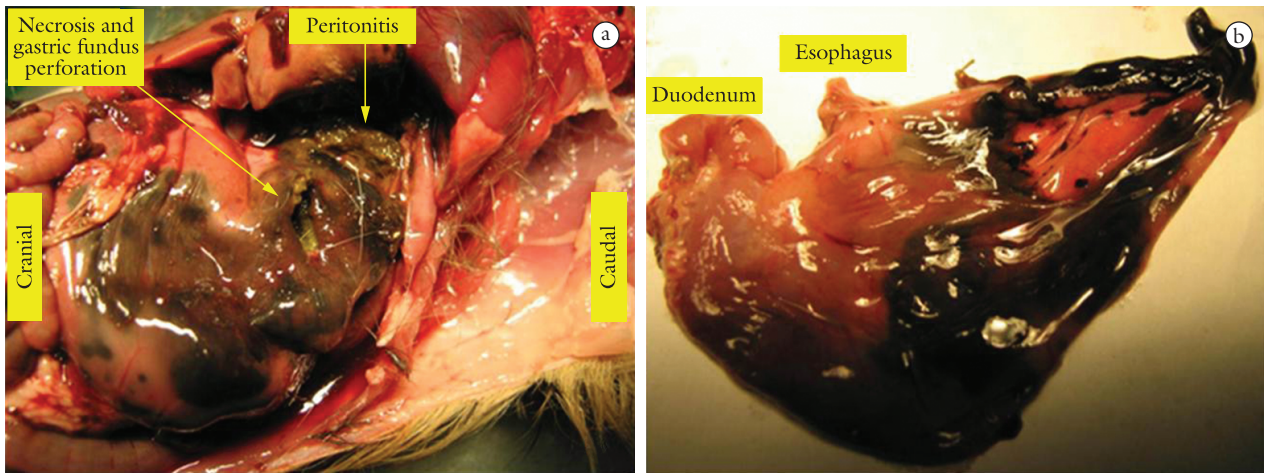
Pre-operative disinfection in guinea pigs should be particularly careful, as in this species antibiotics can selectively destroy gram positive enteral bacteria, resulting in overgrowth of gram negative bacteria and potentially

endotoxemia. (CUNLIFFE-BEAMER, 1993; MORRIS, 1995) To disinfect guinea pigs' skin, either alcohol or surgical iodine are most often used (BROWN, PEARSON and TOMSON, 1993; RUTALA and WEBER, 2008).

## 2 Case report

An adult male guinea pig, of the *Cavia porcellus* strain, weighing 500 grams, acquired in the animal house of the Agronomic Station in Lisbon, was used in a comparative study on gastric microcirculation between the guinea pig and the human. This study was approved by the Scientific and Ethical Committee at the authors' institution.

In this study, the adjustment period of the guinea pigs to the animal house was 2 weeks, having been housed in groups of 2, in cages MAC IV<sup>®</sup>, with an area of 1800 cm<sup>2</sup>. The environmental monitoring included room temperature of 24 °C, humidity 45% to 65%, light cycle of day/night of 12 hours, enrichment of the cage guard, cleaning and daily maintenance of facilities, with disposal of excreta by running water.



**Figure 1.** Gross appearance of the abdominal cavity after laparotomy. a) Gangrene of the gastric fundus with rupture and peritonitis. b) Extensive destruction of the gastric fundus.

The guinea pigs were given 2-hour permanence on the premises of the operating room, in non-operating hours, for 2 days, for prophylaxis of stress and adaptation to the environment of the operating room, after which the animals were returned to the animal house.

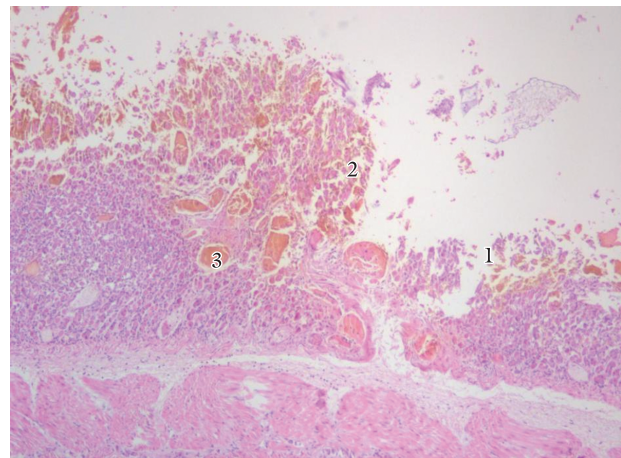
The welfare of the animals, in its multiple aspects, was assured by the technical staff at our institution. Guinea pigs were fed ad libitum with filtered water, clover hay, fresh herbs (dandelion) and vegetables rich in vitamin C (100 g/day) and vitamin C supplement daily (20 micrograms directly per os).

According to the design of the project, the senior author (J.G.) performed a Nissen procedure in an adult male guinea pig. The operation was performed through a 6 cm-long upper median laparotomy. The spleen and the gastric fundus were pulled, in order to perform the lysis of the adhesions of the stomach to the adjacent structures, and to carry out ligation of the proximal short vessels, with a Covidien LigaSure Precise® forceps. Subsequently, after identifying the esophagus gastric junction and making an opening in the lesser omentum pars flaccida, the retro esophageal passage of the gastric fundus was approached and a floppy fundoplication with two 2.5 mm long stitches of silk 4/0 was performed.

Having occurred accidental contamination of the operative field, a swab soaked with Betadine cutaneous solution (10%) was passed over the serosa of the anterior wall and fundus of the stomach.

The operation was completed with abdominal closure in two layers: the deep muscular and fascial layer, with continuous polyamide suture 4/0, and the superficial cutaneous layer, with continuous nylon suture 4/0. After skin closure, a sprayable plastic film bandage was applied. The recovery from the anesthesia was uneventful.

However, the guinea pig died 12 hours postoperatively. At necropsy, the examination of the skin and of the mucous membranes was unremarkable, including the integrity of the surgical scar. The thoracic organs were normal at gross inspection of the thoracic cavity, after symmetric bilateral thoracotomy, through the middle axillary lines, and elevation of the thoracic wall from the sternal notch to the diaphragm. The abdominal cavity was exposed, extending the anterior



**Figure 2.** Histopathological specimen of the gastric fundus, stained with hematoxylin-eosin, showing: 1) necrosis and sloughing of the gastric epithelium, from the fundus to the body; 2) presence of squamous cells with picnotic small and black nuclei – cariorexis and karyolysis; 3) presence of eosinophilic cells and very brown pigment in the stomach wall, corresponding to povidone-iodine.

thoracic wall flap through the abdominal wall till the pelvic region, after anterior disinsertion of the diaphragm.

At gross inspection, the peritoneal cavity showed extensive peritonitis secondary to leakage of gastric contents, as a result of extensive gangrene with rupture of the proximal stomach (Figure 1). There was neither haemoperitoneum nor any abnormality in the other abdominal organs.

The histopathologic diagnosis (performed by Fernanda Cabrita, MD) documented: 1) necrosis and sloughing of the entire gastric epithelium, from the fundus to the body; 2) presence of squamous cells with picnotic small and black nuclei – cariorexis and karyolysis; 3) presence of eosinophilic cells and of brown pigment (Betadine) (Figure 2). The cause of death was deemed to be acute necrotizing hemorrhagic gastritis of the esophagus gastric junction and of the gastric fundus.

### 3 Discussion

The widely used Betadine® is an organic compound composed of a synthetic polymer (povidone, also called polyvinylpyrrolidone) combined with diiodine (I<sub>2</sub>). Povidone enables the diiodine to be dissolved and acts as a reservoir for the iodine that is gradually released (CASTEL, CASADO and MICALI, 2012). Diiodine is the antiseptic component. Due to its small size and lack of charge, it easily penetrates the cell walls of bacteria and fungi, following the same route taken by sugars, amino acids and other metabolites (BURKS, 1998; CASTEL, CASADO and MICALI, 2012). Diiodine acts as a powerful oxidant that causes disruption of protein and nucleic acid structure and synthesis. Many viruses, protozoa, yeasts, cysts and spores are also susceptible (BURKS, 1998).

The most commonly used form of Betadine® is the 10% Betadine® dermic solution composed of a povidone-iodine 10 g/100 mL (corresponding to 1g of active diiodine), and other constituents, including glycerol, nonoxynol 9, disodium phosphate dehydrate, potassium iodate, citric acid monohydrate, sodium hydroxide, and purified water (BURKS, 1998; CASTEL, CASADO and MICALI, 2012).

In animal experimental surgical procedures, povidone-iodine is frequently used to prevent infection and clean contaminated wounds. (BAUMANS, REMIE, HACKBARTH et al., 2006) In human medicine it is also widely used not only for skin disinfection (VEIGA, DAMASCENO, VEIGA FILHO et al., 2008; CASTEL, CASADO and MICALI, 2012), but also to help control infections in body cavities like the pleural and abdominal cavities (WHITESIDE, TYTHERLEIGH, THRUSH et al., 2005; FINDIK, GEZER, AYDOGDU et al., 2010).

In fact, several authors have even reported a protective role of this antiseptic, minimizing skin necrosis after thermal and chemical insults to guinea pigs' skin (WORMSER, SINTOV, BRODSKY et al., 2000; WORMSER, BRODSKY and REICH, 2002; BRODSKY, ERLANGER-ROSENGARTEN, PROSCURA et al., 2008). Other authors have proved povidone-iodine to be both safe and effective in guinea pigs in the reduction of bacterial growth and adherence to urothelium (GASSER and MADSEN, 1993). Others yet have shown that povidone-iodine is effective in reducing bacterial counts in a guinea pig model after induced contaminated skin lacerations (HOWELL, STAIR, HOWELL et al., 1993).

However, povidone-iodine exposure to guinea pigs has been proved to be locally toxic in other contexts, namely in the middle ear of guinea pigs (ICHIBANGASE, YAMANO, MIYAGI et al., 2011). Moreover, in vitro studies showed povidone-iodine solutions to be toxic to granulocytes, to monocytes and to conjunctiva cells in such small concentrations as 0.05% (IWASAWA and NAKAMURA, 2003; VAN-DEN-BROEK, BUYS and VAN-FURTH, 1982). Higher concentrations, including the 10% concentration that is commonly used in experimental settings, were found to be cytotoxic to all fibroblasts in culture dishes (BURKS, 1998). Interestingly, it has been shown in a model of microcirculation in the hamster cheek pouch that exposure to 1% povidone-iodine solution for one hour resulted in complete cessation of blood flow in surface capillaries that did not resume for 60 minutes

(BRINEMARK, ALBREKTSSON, LINDSTRÖM et al., 1966; BURKS, 1998). Finally, there have also been a few anecdotal reports of systemic toxicity, including renal failure, with povidone-iodine use in wounds. (BURKS, 1998)

In conclusion, the authors believe that this case report, as well as the bibliographic references alluded to, suggest that although safe in most cases, the use of povidone-iodine cutaneous solution (10%) in guinea pigs, can be toxic. As far as the authors could determine, this is the first time in the literature that the topical application of a povidone-iodine solution applied to the abdominal contents of a guinea pig is associated with intra-abdominal necrosis. This knowledge can help refining protocols involving animal models, as well as improving future experimental designs.

**Acknowledgements:** One of the authors (Diogo Casal) received a grant from The Program for Advanced Medical Education, which is sponsored by Fundação Calouste Gulbenkian, Fundação Champalimaud, Ministério da Saúde e Fundação para a Ciência e Tecnologia, Portugal.

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Received June 12, 2012  
Accepted March 3, 2013