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Injury due to extravasation of thiopental and propofol: Risks/effects of local cooling/warming in rats

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ABSTRACT

Inadvertent leakage of medications with vesicant properties can cause severe necrosis in tissue, which can have devastating long-term consequences. The aim of this study was to evaluate the extent of extravasation injury induced by thiopental and propofol, and the effects of cooling or warming of local tissue on extravasation injury at macroscopic and histopathologic levels. Rats were administered intradermally thiopental (2.5 mg/100 μL) or propofol (1.0 mg/100 μL). Rats were assigned randomly to three groups: control (no treatment), cooling and warming. Local cooling (18–20 °C) or warming (40–42 °C) was applied for 3 h immediately after agent injection. Lesion sizes (erythema, induration, ulceration, necrosis) were monitored after agent injection. Histopathology was evaluated in skin biopsies taken 24 h after agent injection. Thiopental injection induced severe skin injury with necrosis. Peak lesions developed within 24 h and healed gradually 18–27 days after extravasation. Propofol induced inflammation but no ulceration, and lesions healed within 1–2 days. Local cooling reduced thiopental- and propofol-induced extravasation injuries but warming strongly exacerbated the skin lesions (e.g., degeneration, necrosis) induced by extravasation of thiopental and propofol. Thiopental can be classified as a "vesicant" that causes tissue necrosis and propofol can be classified as an "irritant". Local cooling protects (at least in part) against skin disorders induced by thiopental and propofol, whereas warming is harmful.

1. Introduction

Accidental leakage of certain medications into the body from an intravenous drip is not uncommon. Inadvertent leakage of medications with vesicant properties can cause severe necrosis in tissue, which can have devastating long-term consequences. Most instances of extravasation are attributed to cytotoxic agents, and the prevalence has been reported to be 0.1–6% [1,2]. In addition, several non-cytotoxic agents have been reported to possess vesicant properties due to their high osmolarity, extremely acidic or basic pH, and vasoconstrictive activity [3]. Several guidelines for overall management of extravasation have suggested that recognition of potential risks for each agent is important so that clinicians can manage extravasation depending on the severity of such risks [4,5]. Intravenous cytotoxic agents can be classified into three categories according to the extent of damage from extravasation: vesicants, irritants, and non-tissue-damaging agents [1,2,4]. Vesicants can cause tissue necrosis even at small volumes of extravasation because they are inherently toxic to cells. Irritants can cause an inflammatory reaction (but not necrosis) at the extravasation site. Non-tissue-damaging agents do not damage tissue at all.

Thiopental and propofol are used for the induction and maintenance of anesthesia. Extravasation of these agents is common because anaesthetized patients cannot indicate pain during injection [6]. Risk of extravasation injury is increased because propofol is administered forcefully using automated syringe drivers. Several case reports from 1961 through to 2014 have highlighted extravasation by thiopental or propofol [3]. It is well known that thiopental can act as a vesicant [7] and propofol can act as an irritant [8–11]. However, few reports have shown the vesicant effects of propofol [12–14]. Thus, the risk of skin lesions induced by propofol extravasation is understood incompletely because data

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are limited to a few case reports. Clinicians manage extravasation injuries according to the potential risks of agents. Hence, classification of non-cytotoxic agents into the three categories described above (as well as cytotoxic agents) depending on their toxicity would be useful.

Prompt interdisciplinary management of tissue damage induced by extravasated agents is important for successful therapy. Several reports have shown that stopping the drug infusion as well as surgical excision, thermal application and/or pharmacologic interventions aid management of injury due to extravasation of agents [4,5]. Cooling or warming of local tissue are major supportive measures to reduce skin lesions induced by certain agents [1,3,4,15]. According to one overview of extravasation management [16], hospitals should ensure the availability of "extravasation kits containing cold–hot packs" at the treatment unit. However, there is little scientific basis for the effects of poultices on skin lesions. With regard to management of thiopental extravasation, warming is recommended by the manufacturer, though there is no evidence to indicate therapeutic effects. With respect to management of propofol extravasation, only one report has shown that cooling reduces pain [17]. Thus, the usefulness of cooling or warming of local tissue to manage injuries induced by extravasation of thiopental or propofol is not known.

In the present study, we first evaluated the extent of extravasation injuries induced by thiopental or propofol and classified these agents (as well as cytotoxic agents) on the basis of macroscopic and histopathologic evaluations of skin damage. Next, the effects of local cooling or warming on extravasation injury were evaluated to provide a comprehensive view of management strategies for extravasation of thiopental and propofol.

2. Materials and methods

2.1. Animals

All experiments were carried out in accordance with the *Guide for Animal Experimentation from the Committee of Research Facilities for Laboratory Animal Sciences of Hiroshima University* (permit number: A15-31).

Thirty-three male Wistar albino rats (8 weeks; body weight, 250–270 g) were obtained from Japan SLC, Inc. (Shizuoka, Japan). Rats were housed in individual cages in a temperature-controlled room at 23 °C on a 12-h light–dark cycle. They were fed a standard laboratory diet (MF, Oriental Yeast Company, Tokyo, Japan) and water *ad libitum* for >1 week before experimentation.

2.2. Extravasation models

Rats were anesthetized with pentobarbital (40 mg/kg, i.p.). According to a previous report [18], the hair on the back of rats was shaved with an electrical clipper (Thrive 2100; Daito Electric Machine Industry Co. Ltd., Osaka, Japan). Sodium thiopental (Ravonal®; Tanabe–Mitsubishi, Osaka, Japan) was dissolved at 2.5 mg/100 μL in water for injection according to manufacturer instructions. Twenty-four hours after hair removal, rats with no wounds were injected intradermally (i.d.) with a solution of thiopental or propofol (1.0 mg/100 μL of Diprivan®; AstraZeneca, Osaka, Japan) at 100 μL (the minimum volume at which lesions can be observed macroscopically). As a negative control group, physiologic (0.9%) saline was injected (i.d.) at 100 μL as well as thiopental and propofol. Intradermal injections were undertaken after grabbing dorsal skin using a 26-G needle at the center of a hair-free site 7 cm from the ear. Two injections were made on the axisymmetric dorsal side of each rat. Right-side lesions were monitored until the injury healed completely. Left-side lesions were punch-biopsied (using a dermal punch) 24 h after intradermal injection for histopathologic evaluation under anesthesia with pentobarbital.

2.3. Cooling and warming of local tissue

Rats that had undergone intradermal injection of thiopental or propofol were assigned randomly to three experimental groups of 5 rats each: no treatment (control); cooling (treatment with a cold pack); warming (treatment with a hot pack). Cooling and warming of local tissue were done for 3 h immediately after intradermal injection using cold or hot packs (3M HealthCare, Tokyo, Japan), respectively [19]. Three rats were assigned to a group in which saline was injected via the intradermal route without treatment. Skin temperature was monitored every 10 min using electronic thermocouple probes (BTM-4208SD; Sato-Tech, Kanagawa, Japan), and was maintained at 18–20 °C or 40–42 °C for cooling and warming, respectively.

2.4. Macroscopic evaluation

Extravasation injury to skin was evaluated macroscopically according to a method described previously [18]. Briefly, the widest perpendicular diameters of skin lesions were measured using a caliper by an investigator blinded to group allocation. Each lesion site was inspected every day during the first week after intradermal injection, then every 5 days from day-7. Four parameters of lesions (erythema, induration, ulceration, necrosis) were assessed. The area of lesion sites was calculated in cm^2 as the product of diameters [18]. The area under the lesion–time curve (AUC) was calculated in cm^2 days using the trapezoidal method [18]. The AUC, peak area of the lesion, and damage duration were analyzed until the injury healed completely.

2.5. Histopathologic evaluation

Lesion sites were biopsied (using a dermal punch) with a diameter of 4 mm at 24 h after intradermal injection according to the peak time of lesions using phenytoin (which is thought to possess strong alkaline properties similar to those of thiopental) [20]. Tissue samples were suspended in 10% formaldehyde for fixation before dehydration, Sections (5 μm) from the paraffin-embedded tissue blocks were stained with hematoxylin and eosin, in addition to standard histopathologic evaluation under a light microscope (BX51; Olympus, Tokyo, Japan). Each sample was analyzed by independent pathologists blinded to the experimental procedure.

2.6. Statistical analyses

Data are the mean $\pm$ standard error of the mean (SEM). Differences among each treatment group were analyzed using Kruskal–Wallis test followed by the Student Newman–Keuls multiple-comparison *post hoc* test. $P<0.05$ was considered significant.

3. Results

3.1. Macroscopic findings

For saline-injected rats, no change was observed at any injection site. In thiopental-treated rats, skin lesions developed immediately and reached maximal intensity within 24 h after injection (Fig. 1a). At 2–3 days after thiopental injection, the epidermis had regenerated and exhibited eschar formation, granulation and excoriation of necrotic sites. Typical shape of these skin lesions was ovoid, and induration, erythema, and ulceration (in descending order of size) were observed. Epidermal integrity was