Regular Article

Evaluation of Risk of Injury by Extravasation of Hyperosmolar and Vasopressor Agents in a Rat Model

Yuuka Shibata,*[a] Yumeka Sagara,[b] Tomoharu Yokooji,[b] Takanori Taogoshi,[a] Maiko Tanaka,[c] Michihiro Hide,[d] and Hiroaki Matsuo[a]

[a] *Department of Pharmaceutical Services, Hiroshima University Hospital; 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan:* [b] *School of Pharmaceutical Sciences, Hiroshima University; 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan:* [c] *Department of Dermatology, Mazda Hospital; 2–15 Aosakiminami, Fuchu-cho, Aki-gun, Hiroshima 730–8670, Japan: and* [d] *Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University; 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan.*

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Inadvertent leakage of noncytotoxic agents causes severe tissue injury. In this study, we macroscopically and histopathologically evaluated the extent of skin injury caused by extravasation of hyperosmolar or vasopressor agents in rats. Rats were intradermally administered saline (100 μL), the hyperosmolar agents mannitol (5–20 mg/100 μL) and glucose (5–50 mg/100 μL), or the vasopressors dopamine (2 mg/100 μL), adrenaline (0.1 mg/100 μL), and noradrenaline (0.1 mg/100 μL). Lesion size (erythema, induration, ulceration, and necrosis) was monitored after agent injection. Skin tissue biopsies were evaluated at 24 h after agent injection. Mannitol and glucose induced severe lesions in a concentration (and osmolarity)-dependent manner. Mannitol and glucose at 10–20% (w/v) induced inflammation, and lesions healed within 3–6 d. In contrast, ≥25% (w/v) glucose elicited severe skin lesions with ulceration and necrosis within 24 h, which healed gradually 16–22 d after injection. The severity of extravasation injury caused by vasopressors varied. Adrenaline and noradrenaline induced severe injury with ulceration and necrosis, which healed over 23.3 and 18.3 d, respectively. In contrast, dopamine induced erythema and induration, and damage duration was only 5.7 d. In conclusion, mannitol and glucose at osmolarities of 549–1098 and 833–1110 mOsm/L, respectively, can be classified as "irritants," while ≥1388 mOsm/L glucose can be classified as a "vesicant." As for vasopressors, adrenaline and noradrenaline can be classified as "vesicants" whereas dopamine can be classified as an "irritant."

Key words extravasation; vasopressor; hyperosmolar; noncytotoxic

Inadvertent vascular leakage of medications is a major iatrogenic cause of injury, especially severe tissue injury. Most instances of extravasation injury are caused by cytotoxic agents. Therefore, several guidelines have been issued on the prevention and treatment of extravasation injury by cytotoxic agents. In these guidelines, cytotoxic agents are classified into three categories according to the severity of skin injury after extravasation: vesicants, irritants, and non-tissue-damaging agents.[1–3] Vesicants are agents that cause tissue necrosis even at small volumes of extravasation owing to their inherent toxicity to cells. Irritants cause inflammation without necrosis at the extravasation site. Non-tissue-damaging agents do not induce tissue injury at all. By careful monitoring according to severity of potential iatrogenic effects, the incidence of extravasation injury induced by cytotoxic agents has decreased.[3] In contrast, the number of case reports of severe extravasation injury caused by noncytotoxic agents are increasing as the mechanism of injury induced by extravasation of noncytotoxic agents is incompletely understood compared with that of cytotoxic agents.

With respect to the mechanism of tissue damage by extravasation of noncytotoxic agents, high osmolarity, acidic or alkaline pH, and/or vasoconstrictive activity have all been suggested as the cause of severe extravasation injury among noncytotoxic agents.[4,5] Mannitol is generally used as an osmotic diuretic agent to increase urinary excretion and reduce elevated intracranial pressure following head injuries.[6] As mannitol solutions (15–20% (w/v)) exhibit hyperosmolarity (824–1098 mOsm/L), extravasated mannitol can cause swelling and severe edema by drawing fluid into the tissue.[7] In addition, extravasation of >10% (w/v) (555 mOsm/L) glucose can cause tissue injury by dysregulating the equilibrium between intracellular and extracellular fluid. Inadvertent leakage of these agents has been reported to cause reduced blood flow, tissue necrosis, and nerve damage.[8] In such cases, emergency fasciotomy, skin grafting, wound debridement, or even limb amputation may be needed.[9,10] Furthermore, hyperosmolar agents are high risk agents for the induction of phlebitis. However, the mechanism of phlebitis might be different from that of extravasation injury. Phlebitis is thought to be caused by the disruption of vascular endothelial cells, whereas extravasation injury is caused by the disruption of dermal cells and skin muscle cells. As many previous reports have revealed the extent to which osmolarity causes phlebitis in peripheral veins,[11,12] the permissible osmolarity for peripheral intravenous transfusions was determined based on the prevention of phlebitis in clinical situations. However, it is unclear what osmolarity causes extravasation injury.

Catecholamines such as dopamine, adrenaline and noradrenaline are commonly used as vasopressors in emergencies to improve critical hemodynamic instability. The American Heart Association guidelines recommend the use of a central venous line for catecholamine administration to prevent extravasation injury.[13] However, in emergencies, catecholamine may be administered using a peripheral line, as a peripheral line is more easily available compared with a central venous

* To whom correspondence should be addressed. e-mail: utatti@nifty.com

line, and critical hemodynamic instability should be improved as soon as possible. Furthermore, catecholamines are forcefully administered by constant infusion using automated syringe drivers, except for when administered as a single intravenous bolus injection against cardiac arrest. Thus, the risk of extravasation injury induced by catecholamines may be relatively high. However, the extent of extravasation injuries is incompletely understood because data are limited to a few case reports. Hence, it is important to recognize the potential risks for tissue injury caused by extravasation of nontoxic agents. In this study, we macroscopically and histopathologically evaluated the extent of extravasation injuries induced by hyperosmolar agents and vasopressors using a rat model. Moreover, we classified these agents into three categories (irritants, vesicants, or non-tissue damaging agents) based on the degree of skin damage.

MATERIALS AND METHODS

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). Fifty-four male Wistar rats (8 weeks old; body weight, 250–270 g) were purchased 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 received a standard laboratory diet (MF, Oriental Yeast Company, Tokyo, Japan) and water *ad libitum* for >1 week before experiments.

Extravasation Models Rats were anesthetized with medetomidine (0.15 mg/kg), midazolam (2.0 mg/kg), and butorphanol (2.5 mg/kg) injected intraperitoneally. Extravasation studies were performed according to previous reports.[14,15] Briefly, rats were assigned randomly to eighteen experimental groups of three rats each. The hair on their backs was shaved with electrical clippers (Thrive 2100; Daito Electric Machine Industry Co., Ltd., Osaka, Japan). Twenty-four hours after hair removal, rats with no wounds were injected intradermally (i.d.) with 100 μL of hyperosmotic agent or vasopressor (the minimum volume at which lesions can be observed macroscopically). As a negative control group, 100 μL physiological (0.9%) saline (pH 4.5–8.0) was injected i.d. To evaluate the effect of osmotic pressure on the severity of extravasation injury, mannitol (Yoshindo Inc., Toyama, Japan) and glucose (Otsuka Pharmaceutical Factory Inc., Tokushima, Japan) were used as pharmacologically inactive, noncytotoxic agents. Twenty percent (w/v) mannitol and 50% (w/v) glucose were diluted to 5–15% (w/v) and 5–40% (w/v) with water for injection, respectively. When their osmolarities were calculated, 20% (w/v) mannitol and 50% (w/v) glucose have osmolarities of 1098 and 2775 mOsm/L, respectively. Clinical concentrations of the vasopressors dopamine (20 mg/mL, pH 3.0–5.0; Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan), adrenaline (1 mg/mL, pH 2.3–5.0; Daiichi Sankyo Co., Ltd., Tokyo, Japan), and noradrenaline (1 mg/mL, pH 2.3–5.0; Daiichi Sankyo Co., Ltd.) were used. To exclude the effect of pH on extravasation injury, saline solution was adjusted to pH 3.0 and 5.0 with hydrochloric acid and injected as controls. Intradermal injections using a 26-G needle were performed after pinching the dorsal skin at the center of a hair-free site 7 cm from the ear. Two injections were made, on axisymmetric dorsal sides of each rat. Right-hand side lesions were macroscopically monitored until the injury healed completely. Left-hand side lesions were punch-biopsied under anesthesia using a dermal punch (Maruho, Osaka, Japan) with a diameter of 4 mm at 24 h after intradermal injection in accordance with the peak time of lesion severity in a previous report on histopathological evaluation of extravasation injury.[16]

Macroscopic Evaluation Extravasation injury to skin was evaluated macroscopically according to a previously described method.[14] Briefly, the widest perpendicular diameters of skin lesions were measured using a caliper. The area of lesion sites was calculated in cm^2 as the product of diameters.[14] Each lesion site was inspected every day during the first week after intradermal injection, then every 5 d from day 7. Four lesion parameters (erythema, induration, ulceration, necrosis) were assessed. The area under the lesion–time curve (*AUC*) was calculated in cm^2 days using the trapezoidal method.[14] The *AUC*, peak area of the lesion, and damage duration were analyzed until the injury healed completely.

Histopathological Evaluation Tissue samples obtained by biopsy were fixed in 10% formaldehyde before dehydration, then sections (5 μm thick) from the paraffin-embedded tissue blocks were stained with hematoxylin and eosin and evaluated under a light microscope (BX51; Olympus, Tokyo, Japan). Each sample was analyzed by independent pathologists blinded to the experimental procedure.

Statistical Analyses Data are presented as the mean± standard deviation (S.D.). Differences among treatment groups were analyzed using ANOVA followed by the Student–Newman–Keuls multiple-comparison *post hoc* test. A value of $p<0.05$ was considered to indicate statistically significant differences.

RESULTS

Macroscopic Findings Saline-injected rats showed slight erythema at injection sites that disappeared within 1.3 d (Table 1). Mannitol or glucose injection immediately induced ovoid swollen skin lesions that reached maximal size within 24 h. In these rats, mannitol or glucose administration induced severe lesions, such as ulceration, in a concentration (and osmolarity)-dependent manner (Table 1). Mannitol and glucose at ≤20% (w/v) induced erythema, but no ulceration, and erythema lesions healed within 0.7–6 d. In contrast, ≥25% (w/v) glucose elicited severe skin lesions with ulceration within 24 h that healed 17–22 d after injection. In mannitol-injected rats, the peak area and *AUC* of lesions increased significantly at ≥15% (w/v) and the damage duration was extended at ≥10% (w/v) compared with the saline-injected rats. In contrast, in glucose-injected rats, the peak area of lesions also increased significantly at ≥15% (w/v), but extended duration of damage was observed only at ≥25% (w/v). These results indicate that glucose-induced lesions were slightly less severe compared with those induced by mannitol at the same concentration.

Next, we examined the extent of extravasation skin injury induced by three vasopressors; dopamine, adrenaline and noradrenaline. All vasopressors induced maximal skin lesions within 24 h and the peak area was similar among the three agents (Table 2). However, the severity of extravasation injury differed. Dopamine induced erythema and induration, with no ulceration, which healed within 5.7 d, whereas adrenaline and

Table 1. Effects of Osmolarity on Mannitol- and Glucose-Induced Skin Lesions in Rats

Agents	Concentration (% (w/v))	Osmolarity (mOsm/L)	Macroscopic findings	Histopathological findings	Peak area (cm^2)	*AUC* (cm^2 d)	Damage duration (d)
Saline	0.9	286	E	NC	0.14±0.14	0.16±0.16	1.3±1.2
Mannitol	5	274	E	NC	0.24±0.04	0.35±0.14	2.3±0.6
	10	549	E	ES, IIC	0.36±0.17	0.77±0.32	5.7±0.6**
	15	823	E	ES, IIC	0.47±0.02**	1.04±0.46*	5.3±1.5**
	20	1098	E	ES, IIC	0.54±0.06**	0.97±0.30*	3.7±0.6*
Glucose	5	278	E	NC	0.04±0.07	0.05±0.09	0.7±1.2
	10	555	E	ES, IIC	0.28±0.05	0.44±0.11	3.3±0.6
	15	833	E	ES, IIC	0.38±0.03*	0.82±0.45	5.0±2.6
	20	1110	E	ES, IIC	0.55±0.07**	0.93±0.42	3.3±1.2
	25	1388	E, I, U	ES, IIC, DCF, NEC	0.59±0.05**	2.40±0.23**	16.7±5.8**
	30	1665	E, I, U	ES, IIC, DCF, NEC	0.52±0.07**	2.53±0.50**	16.7±2.9**
	40	2220	E, I, U	ES, IIC, DCF, NEC	0.50±0.10**	4.30±1.17**	21.7±5.8**
	50	2775	E, I, U	ES, DCF, NEC	0.51±0.14**	5.01±1.49**	21.7±2.9**

Abbreviations: *AUC*, area under the lesion–time curve; E, erythema; I, induration; U, ulceration; NC, no change; ES, epidermal shedding; IIC, infiltration of inflammatory cells; DCF, degeneration of collagen fibers; NEC, necrosis. Each hyperosmolar agent was administered intradermally at a volume of 100 μL. Lesions were monitored until the injury was completely healed. Each value represents the mean±S.D. of results from three rats. *$p<0.05$, **$p<0.01$ compared with saline treated rats.

Table 2. Evaluation of Extravasation Injuries Induced by Vasopressors or Low pH Solution in Rats

Agents	pH	Macroscopic findings	Histopathological findings	Peak area (cm^2)	*AUC* (cm^2 d)	Damage duration (d)
Saline	4.5–8.0	E	NC	0.14±0.14	0.16±0.16	1.3±1.2
Dopamine (20 mg/mL)	3.0–5.0	E, I	ES, IIC	0.37±0.22	0.36±0.09	5.7±3.8
Adrenaline (1 mg/mL)	2.3–5.0	E, I, U	ES, IIC, DCF, NEC	0.32±0.07	2.60±0.62**	23.3±2.9**
Noradrenaline (1 mg/mL)	2.3–5.0	E, I, U	ES, IIC, DCF, NEC	0.35±0.10	3.01±1.01**	18.3±2.9**
Saline pH 3.0	3.0	E	NC	0.16±0.11	0.13±0.07	2.0±1.0
Saline pH 5.0	5.0	E	NC	0.04±0.07	0.04±0.07	0.7±1.2

Abbreviations: *AUC*, area under the lesion–time curve; E, erythema; I, induration; U, ulceration; NC, no change; ES, epidermal shedding; IIC, infiltration of inflammatory cells; DCF, degeneration of collagen fibers; NEC, necrosis. Saline with a pH of 3.0 or 5.0 was prepared by adding hydrochloric acid. Each solution was administered intradermally at a volume of 100 μL. Lesions were monitored until the injury was completely healed. Each value represents the mean±S.D. of results from three rats. **$p<0.01$ compared with saline treated rats.

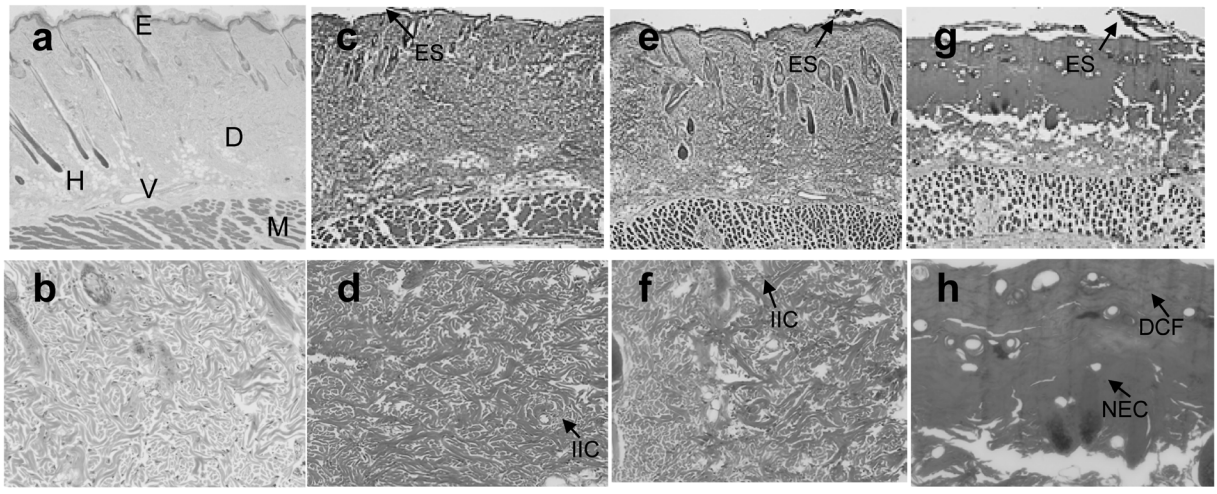

Fig. 1. Histopathology of Skin Lesions Induced by Extravasated Mannitol or Glucose in Rats

Control skin (a, b) after intradermal (i.d.) injection of saline shows complete architectural construction of dermis, skin appendixes, epithelium (E), dermis (D), muscle (M), hair follicles (H), and vessels (V). Injection of both mannitol (c, d) and glucose (e, f) at 15% (w/v) resulted in epidermal shedding (ES), and infiltration of inflammatory cells (IIC) into dermis and skin muscle, but no necrosis (NEC). Glucose at 50% (w/v) (g, h) caused ES, degeneration of collagen fibers (DCF) and NEC in the deep dermis and muscle. Skin tissues were biopsied at 24 h after i.d. injection of saline, mannitol, or glucose. Hematoxylin and eosin staining: (a, c, e, g) magnification ×4; (b, d, f, h) magnification ×20. Arrows point to the site of lesions.

noradrenaline induced ulceration, with a duration of 23.3 and 18.3 d, respectively. This suggests that dopamine-induced lesions were much milder than those induced by adrenaline and noradrenaline. In this study, we used vasopressors dissolved in an acidic solution: dopamine, pH 3.0–5.0; adrenaline, pH 2.3–5.0; noradrenaline, pH 2.3–5.0. Notably, it has been reported that extravasation of acidic solutions (pH 2.3–5.0) induces skin lesions.[17] To exclude the effect of the acidic pH of

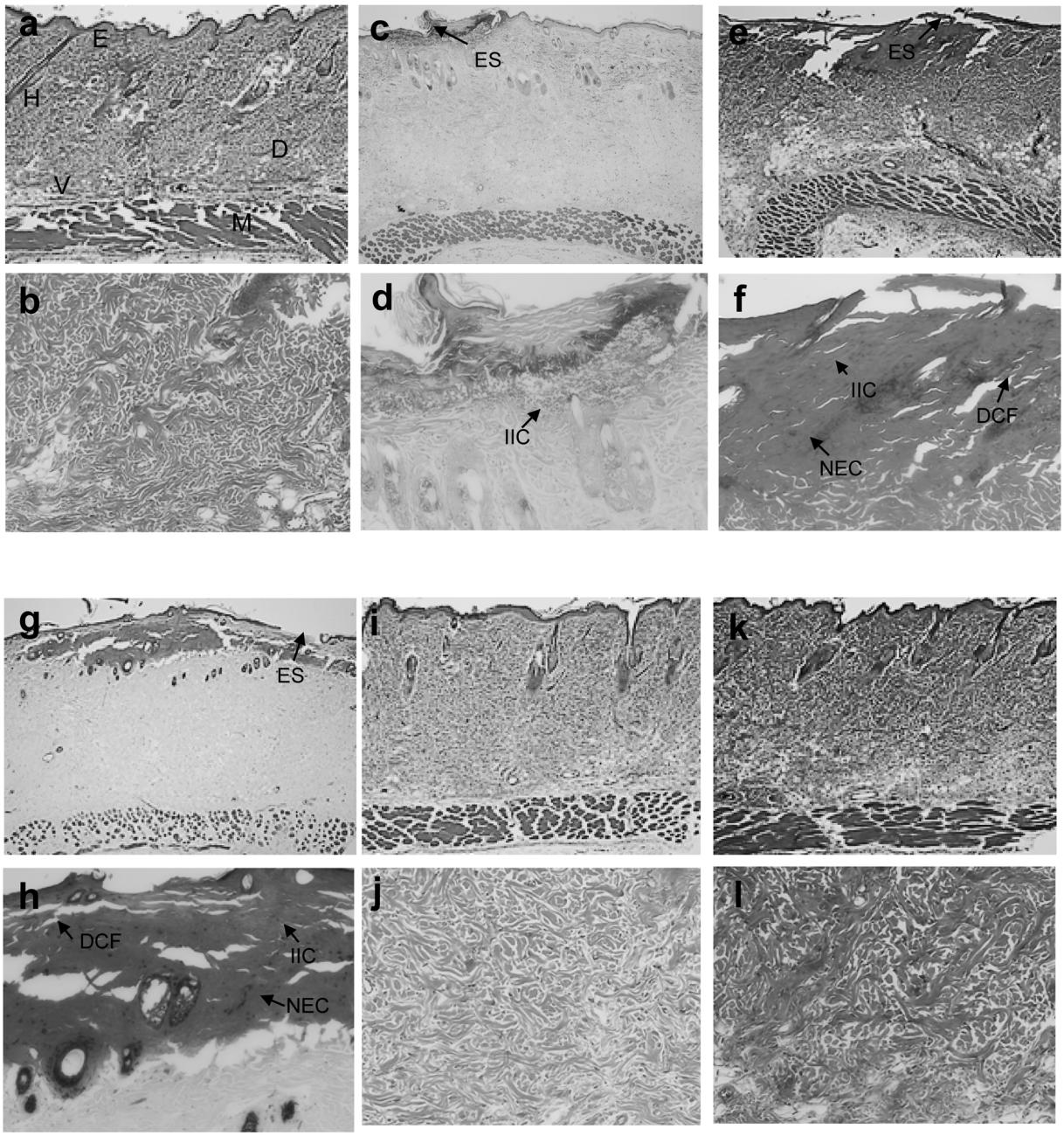

Fig. 2. Histopathology of Skin Lesions Induced by Extravasated Vasopressors in Rats

Control skin (a, b) after intradermal (i.d.) injection of saline shows complete architectural construction of dermis, skin appendixes, epithelium (E), dermis (D), muscle (M), hair follicles (H), and vessels (V). Dopamine injection (c, d) resulted in epidermal shedding (ES), and infiltration of inflammatory cells (IIC) into dermis and skin muscle, but no necrosis (NEC). Adrenaline (e, f) and noradrenaline (g, h) injection caused ES, IIC into dermis and skin muscle, and degeneration of collagen fibers (DCF) and NEC in the deep dermis and muscle. Skin after injection of saline solutions at pH 3.0 (i, j) and 5.0 (k, l) showed complete architectural construction of the dermis. Skin tissues were biopsied at 24 h after i.d. injection of saline or vasopressors. Hematoxylin and eosin staining: (a, c, e, g) magnification ×4; (b, d, f, h) magnification ×20. Arrows point to the site of lesions.

the vasopressor solution on extravasation injury, we confirmed that acidic solutions do not induce extravasation injury. Notably, both pH 3.0 and pH 5.0 saline solutions did not induce indurations or ulcers, although erythema were seen. Furthermore, there were no significant differences in peak area, *AUC*, or damage duration between physiological pH and acidic pH saline solutions.

Histopathological Findings In saline-treated control rats, skin tissue specimens showed normal skin cells with intact architecture (Fig. 1). In good agreement with macroscopic findings, mannitol and glucose at ≤20% (w/v) resulted in epidermal shedding, and inflammatory cell infiltration of dermis and skin muscle, but no necrosis (Table 1, Fig. 1). Notably, collagen degeneration, necrosis, and inflammatory cell infiltration of epidermal, dermal and subcutaneous tissues were evident at 24 h after injection of ≥25% (w/v) glucose (Table 1, Fig. 1). Injections of the three vasopressors caused bleeding, necrosis of vascular endothelial cells, epidermal shedding, and infiltration of inflammatory cells into the dermis and skin muscle. In addition, disruption and degeneration of collagen fibers were also observed in adrenaline- and noradrenaline-injected rats (Fig. 2). Rats injected with physiological pH, pH 3.0, and pH 5.0 saline exhibited regular morphology of skin tissue (Fig. 2). These morphological data are summarized in Table 2.

Table 3. Vesicant Potential of Hyperosmolar and Vasopressor Agents

Agents	Vesicants	Irritants	Non-tissue-damaging agents
Hyperosmolar	Glucose (≥1388 mOsm/L)	Glucose (833–1110 mOsm/L) Mannitol (549–1098 mOsm/L)	—
Vasopressor	Adrenaline (1 mg/mL) Noradrenaline (1 mg/mL)	Dopamine (20 mg/mL)	—

Vesicants are agents that cause tissue necrosis even at small volumes of extravasation owing to their inherent toxicity to cells. Irritants cause inflammation without necrosis at the extravasation site. Non-tissue-damaging agents do not induce tissue injury at all.

DISCUSSION

The Pharmaceuticals and Medical Devices Agency warns that noncytotoxic agents may cause more serious extravasation injuries than cytotoxic agents.[18,19] Previous case reports have shown that hyperosmolar agents and vasopressors cause the most severe extravasation injuries of noncytotoxic agents.[5,10] However, it is unclear what osmolarity and which vasopressors specifically cause these injuries. Pharmacists should manage extravasation injuries according to the potential risks of the agents. In this study, we evaluated the extent of extravasation injuries induced by hyperosmolar agents and vasopressors and classified these agents into three categories depending on their degree of skin injury at macroscopic and histopathological levels using a rat model.

Extravasated hyperosmolar agents cause a shift in fluid from the intracellular to the extracellular space, resulting in dysfunction of cellular membranes and dysregulation of cell volume. High osmotic stress also directly leads to damage of proteins and DNA, formation of reactive oxygen species, and the induction of apoptosis.[4] Because these effects continue until the high osmolarity of extravasated solution reaches an isotonic osmolarity, extravasation of hyperosmolar agents can cause severe skin injuries even in small quantities. In this study, mannitol and glucose induced severe skin lesions in a concentration-dependent manner. At ≥15% (w/v) mannitol/glucose, significantly larger peak areas and *AUC* of lesions with erythema (but no necrosis) were observed compared with saline-injected rats. Furthermore, ≥25% (w/v) glucose elicited severe skin ulceration with collagen degeneration, necrosis, and inflammatory cell infiltration of epidermal, dermal and subcutaneous tissues at 24 h. Concentrations of 15% (w/v) mannitol, 15% (w/v) glucose and 25% (w/v) glucose correspond to osmolarities of 823, 833, and 1388 mOsm/L, respectively. As described already, osmolarity is an important factor influencing phlebitis as well as extravasation injury. To prevent phlebitis, infusion preparations are administered *via* a peripheral vein at approximately 280–1000 mOsm/L.[11,12,20] However, our results suggest that clinicians should consider the development of extravasation injury at approximately 830 mOsm/L, even if this osmolarity is within the range of 280–1000 mOsm/L. In the clinic, 50% (w/v) glucose is administered intravenously *via* a peripheral vein to treat severe hypoglycemia with consciousness disturbance.[21] In our study, glucose at ≥25% (w/v) was classified as a "vesicant" that causes tissue necrosis. Thus, clinicians should carefully monitor for the development of extravasation injury during high glucose infusions at ≥25% (w/v).

In glucose-injected rats, the extent of lesions was slightly milder compared with mannitol-injected rats, even at the same concentration. However, glucose is taken up into cells immediately whereas mannitol is taken up gradually. Thus, the slight differences in the extent of lesions between glucose and mannitol may be due to differences in their diffusibility into cells and metabolism. These results suggest that the degree of extravasation injury induced by hyperosmolar agents also differs according to their uptake and metabolism, even if their osmolarities are the same. By clarifying the mechanism of skin injury due to extravasation in the future, more appropriate treatments can be established for each individual medicine.

Extravasated vasopressors are thought to cause skin injury owing to local ischemia induced by vasoconstriction of veins, capillaries and vasa vasorum. In good agreement with their strength of vasoconstrictor activity, extravasation of adrenaline or noradrenaline induced similar skin lesions, whereas dopamine induced only mild lesions.[22] In future studies we aim to identify the subtypes of the vasopressor receptors involved in extravasation-induced skin injuries. According to the manufacturer's instructions, vasopressors were dissolved in acidic solutions; dopamine pH 3.0–5.0, adrenaline pH 2.3–5.0, and noradrenaline pH 2.3–5.0. Acid exposure commonly causes cellular desiccation, coagulative necrosis, and eschar formation.[17,23,24] Notably, several clinical case reports have shown that extravasation of less tissue invasive agents dissolved in acidic solutions, such as vancomycin (pH 4.0), doxycycline (pH 1.8–3.3), and amiodarone (pH 3.5–4.5), also induces skin lesions.[25–27] However, the effect of acidic pH on extravasation injury may be negligible, as in this study both pH 3.0 and pH 5.0 saline solutions did not induce skin lesions. Thus, the severity of injury induced by extravasated vasopressors might be determined mostly by their strength of vasoconstriction activity, rather than acidity.

In conclusion, osmolarities of 549–1098 mOsm/L mannitol and 833–1110 mOsm/L glucose can be classified as "irritants," while ≥1388 mOsm/L glucose can be classified as a "vesicant." As for vasopressors, adrenaline and noradrenaline can be classified as "vesicants," whereas dopamine can be classified as an "irritant" (Table 3). This information could provide reference values for identification of the risk of extravasation-induced injury by hyperosmolar agents and vasopressors.

Conflict of Interest The authors declare no conflict of interest.

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