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The Effect of Gd-Dimeglumine on Subcutaneous Tissues: A Study with Rats

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Gadopentetate dimeglumine and a saline solution of similar osmolality of 2100 mOs/kg H_2O were placed in the paws and in the thigh muscles and subcutaneous tissue of Sprague-Dawley rats weighing 225–250 g. The paws were serially photographed for 4 weeks and the thighs were examined histologically for up to 4 weeks. Gross and histologic reactions to gadopentetate dimeglumine were greater than those to the saline solution, and included tissue sloughs.

When risk factors for extravascular extravasation are present, such as infusion sites in the dorsum of the hand or foot, or around the ankle, or when soft tissues are obscured by bandages, caution should be exercised when injecting gadopentetate dimeglumine.

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Gadopentetate dimeglumine (Gd) has been an invaluable adjunct in MR imaging. Thus, when we learned of an area of slough on the dorsum of a hand in a patient in whom Gd was injected into an existing line administering IV fluids, we undertook a study of the soft-tissue effects of Gd and compared them with our earlier studies on conventional, low osmolar, and nonionic iodine-containing contrast material [1, 2].

Materials and Methods

Gd and saline of a similar osmolality (2100 mOs/kg H_2O) were compared. The study was approved by the Committee on Humane Care of Laboratory Animals, Washington University School of Medicine. Two groups, each composed of 32 Sprague-Dawley female rats weighing between 225 and 250 g, had each paw injected (128 paws per group) with 0.4 ml of Gd or saline after the administration of intraperitoneal Nembutal. The paws were observed daily for the first week and then weekly for 4 weeks. They were photographed in color at 24, 48, and 72 hr and then weekly for 4 weeks. The reactions in the paws were graded as follows: 1 = mild swelling; 2 = moderate swelling with slight discoloration; 3 = marked swelling, or more discoloration, vesiculation, focal breakdown; and 4 = rank tissue breakdown (Fig. 1). One observer did the photography and graded the reactions and was knowledgeable of the agent injected. Another observer graded the reactions as seen on color slides, but did not know which agent had been injected.

Another 42 rats were divided into two groups, and each of these had each thigh injected intramuscularly with 1 ml of either Gd or saline. The animals were anesthetized with intraperitoneal Nembutal prior to intramuscular injections. They were sacrificed at 24, 48, and 72 hr, and at 1, 2, 3, and 4 weeks. In each time period the six thighs were removed, fixed in formalin, number coded, and examined histologically. The tissue reactions were graded in severity from 0 to 3 in a blinded fashion by one of the authors. The following values were assigned: 1+ = slight but unequivocal inflammatory infiltrate, often as linear arrays of polymorphonuclear leukocytes along septa between fat cells in the dermis, deep soft tissues, or between fascicles of muscle in the deep injection series; 2+ = features of the previous category plus solid aggregates of polymorphonuclear leukocytes at least one high-power microscopic field in diameter; and 3+ = confluent aggregates of polymorphonuclear leuko-

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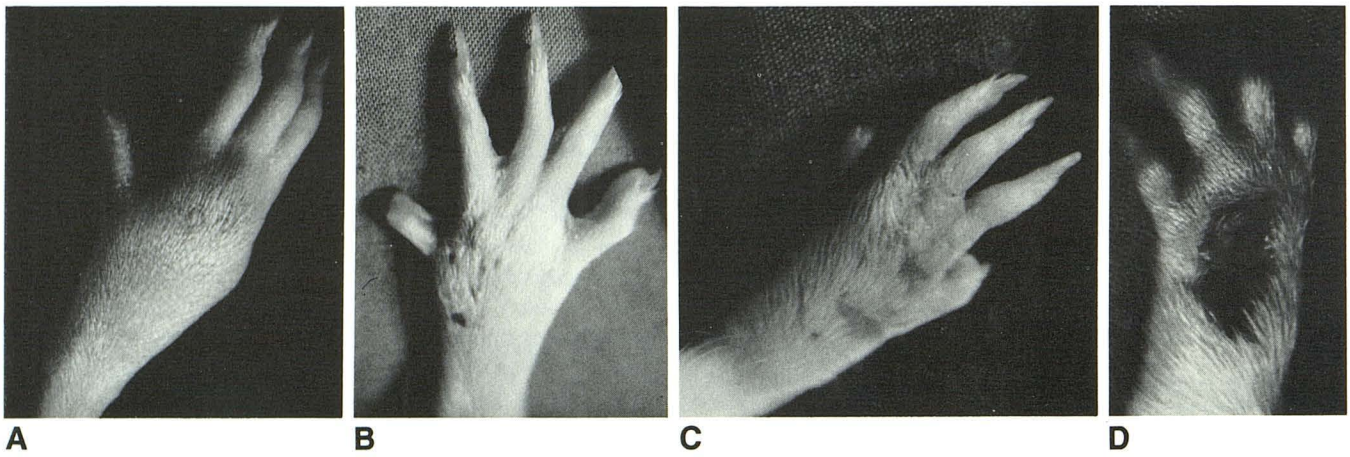

Fig. 1.—Rat paws.
***A*, Grade I: swelling of dorsum of paw. *B*, Grade II: swelling with focal areas of discoloration. *C*, Grade III: swelling with more areas of discoloration. *D*, Grade IV: frank ulceration.**

TABLE 1: Average Numerical Paw Reaction Scores*

Time	Gadopentetate Dimeglumine	Saline 2100
24 hr	183	210
48 hr	173	120
72 hr	166	56
1 wk	232	25
2 wk	212	20
3 wk	124	3
4 wk	11	0
Total score	1101	434

* 32 rats (128 paws) in each group. See text for scoring and statistical analysis.

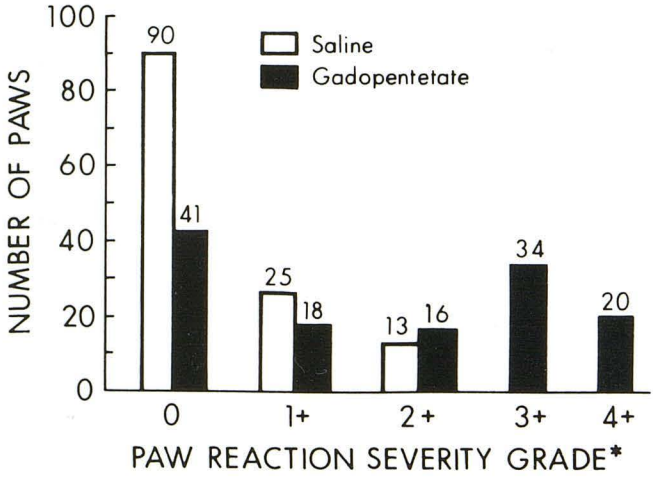

Fig. 2.—Histogram of paw reactions to gadopentetate dimeglumine and saline with osmolality of 2100 at 1 week.

cytes greater than one high-power field in diameter. Complicating lesions such as abscess formation, coagulative necrosis, or appreciable interstitial hemorrhage were noted and were commented on separately.

A similar study of 42 rats divided into two groups involved the subcutaneous injection into each thigh. The number of animals, sacrifice times, and methodology were the same.

The Wilcoxon-Mann-Whitney test was used to compare the mean reaction scores between Gd and control groups. A difference was significant if the *p* value was equal to or less than .05.

Results

The two agents were compared in terms of the severity of the reaction produced in the animals' paws and ranked on our grading system from 1 to 4. The greater the reaction, the higher the score. The average Gd score assigned by the two observers was 1101 (1075 and 1127) and the average saline score was 434 (414 and 455) over the 4-week period (Table 1). The paws that were injected with Gd produced reactions from grade 2 to grade 4 that peaked at 1 week (Fig. 2). The swelling tended to persist and often took up to 4 weeks to resolve. Paw ulceration was seen in 30 of 128 paws injected with Gd and was either focal ulceration (grade 3) or frank ulceration (grade 4). Ulceration did not occur in the group of rats injected with saline, although grade 3 swelling did occur. Gd also produced grade 3 swelling without ulceration. Saline controls exhibited reactions from grade 2 to grade 3 that peaked at 24 hr and was less at 48 and 72 hr. These reactions largely resolved at 1 week.

There was a more severe reaction in the soft tissues to Gd than to saline. With Gd, the histologic inflammatory reactions in the intramuscular and subcutaneous tissues of the thighs persisted with significant effects between 72 hr and 1 week (Figs. 3 and 4). In the case of saline, there was a hyperosmolar histologic effect present for the first 48 hr, but after that the reaction to saline in the tissues largely subsided. Inflammatory reactions were still mildly present at 4 weeks with Gd. No areas of coagulative necrosis, abscess formation, or appreciable interstitial hemorrhage were seen with saline, although these were present with Gd.

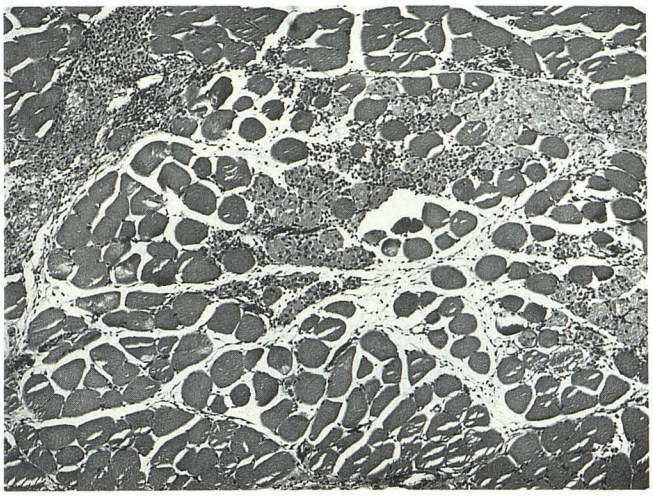

Fig. 3.—Photomicrograph showing marked (3+) inflammatory reaction 3 days after the intramuscular injection of gadopentetate dimeglumine. (H and E ×90)

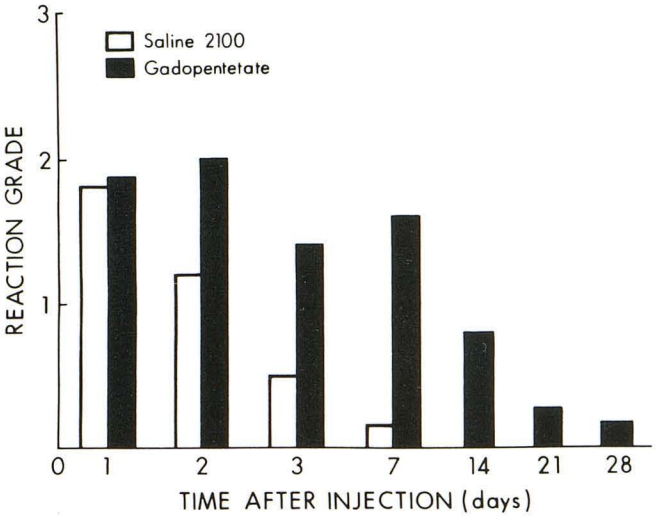

Fig. 4.—Histogram of intramuscular histologic reactions of gadopentetate dimeglumine and saline with osmolality of 2100.

The difference in tissue reaction between Gd and saline was significant at the $p = .05$ level.

Discussion

Gadopentetate dimeglumine (Gd) has proved to be an extremely useful agent in diagnostic radiology; however, it has been associated with some adverse reactions, such as headache, vomiting, hypotension, vaso-vagal reactions, seizures, and local sensations at the injection site. Caution has been urged when using it in patients with severely impaired hepatic or renal function or in those with sickle cell anemia.

Although the amount of Gd that is injected is relatively small compared with iodine-containing contrast agents, our studies suggest that if extravasation occurs in superficial sites such as the dorsum of the hand or foot, a slough could occur as has been seen with iodine-containing contrast materials. The reaction to Gd observed in the paws and noted histologically in the thighs was greater than that seen with saline solution of similar osmolality. However, it was not as severe as the tissue reaction to an ionic iodine-containing medium of similar osmolality, namely Conray 400 [1, 2].

When we compared our studies with earlier ones that we had done with iodine-containing ionic and nonionic contrast agents, it was apparent that the soft tissues were more tolerant of the nonionic and low-osmolar iodine-containing contrast materials than they were of the conventional ionic agents or the Gd [1, 2]. The saline solution of 2100 osmolality produced somewhat more tissue reaction in the paws at 72 hr in the current study than it did in our earlier study [1]. The reason is unclear. Very little soft-tissue effects were noted in control animals injected with saline of osmolalities of 1500 and 750 [1].

When extravasation of Gd does occur, the treatment method is unclear. Clinical and laboratory experience with extravasated systemic chemotherapeutic drugs and medications has suggested the use of hyaluronidase, steroids, topical α-tocopherol, and dimethyl sulfate [3–9]. However, their use when Gd is extravasated has yet to be determined.

In summary, caution should be exercised when injecting Gd when risk factors for extravascular extravasation are present, such as infusion sites in the dorsum of the hand or foot, or around the ankle, or when soft tissues are obscured by tape and bandages.

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