Urological Research 4, 5-8 (1976)

Urological Research

ORIGINALS

Vascular Absorption of Intravesical Formalin in Cyclophosphamide-induced Haemorrhagic Cystitis*

Hans-Udo Eickenberg and Robert Adcock

Section on Urology, Department of Surgery, and Price Institute for Surgical Research, University of Louisville School of Medicine, Louisville, Kentucky, U.S.A.

Received: November 6, 1975

Summary. Haemorrhagic cystitis was induced in dogs by the administration of cyclophosphamide. The bleeding was stopped by intravesical instillation of Formalin. Vascular absorption of formaldehyde was determined by measurement of serum levels. Progressively increasing amounts in apparent relationship to the concentration of Formalin instilled into the bladder were found in all dogs. Higher serum levels were noted in animals with haemorrhagic cystitis induced by cyclophosphamide than in dogs with normal bladders. This study reinforces our clinical impression that formaldehyde is absorbed continuously through the wall of the urinary bladder in dogs and absorption is related to the concentration gradient. These kinetics should be kept in mind when treating patients with intravesical Formalin in order to prevent the systemic effect of the vascular absorption.

Key words: Cyclophosphamide, Haemorrhagic cystitis, Vascular absorption, Formaldehyde.

Formalin, a 37% aqueous solution of formaldehyde, has been used clinically in various concentrations to stop haemorrhage following irradiation, from tumour, and from cyclophosphamide-induced cystitis (8). It is also used to fill the bladder before radical cystectomy (20) to denature tumour cells and has been described as an agent to stimulate the paralysed neurogenic bladder (1). Methenamine hippurate, a urinary antiseptic, produces its antibacterial activity following a breakdown to formaldehyde and ammonia in acid urine (15). A search of the literature, however, fails to disclose any report on the vascular absorption of Formalin from the urinary bladder. The following animal study was set up to determine the kinetics of Formalin absorption through the normal urinary bladder wall and in cyclophosphamide-induced haemorrhagic cystitis.

Single intravenous doses of cyclophosphamide were used to induce haemorrhagic cystitis in dogs, followed by intravesical instillation of Formalin to halt the process, and measurement of the vascular absorption of formaldehyde. This study was designed to investigate the safety of this treatment, as well as to study the effects of Formalin solution in different concentrations on normal bladder mucosa and in cyclophosphamide-induced haemorrhagic cystitis.

MATERIAL AND METHOD

Male dogs weighing 15-25 kg were catheterised with sterile technique under general anaesthesia. Using a rubber band around the penis to prevent leakage, 150 ml of 10% Formalin were instilled into the bladder in the five dogs in Group I. An additional five dogs comprising Group Ia were studied using a 5% Formalin concentration. The catheter was clamped and the Formalin was left in the bladder for 30 minutes. Residual Formalin was then drained from the bladder and the bladder irrigated with normal saline solution. Blood was obtained from peripheral veins before instillation and afterwards at 10-minute intervals for 1 hour. All specimens were assayed for formaldehyde

*This work was supported by American Cancer Society Institutional Research Grant No. 83905-F

levels using the routine laboratory method (9). All dogs had sterile urine and normal renal function.

In Group II, 10 dogs received single intravenous doses of cyclophosphamide 50 mg/kg. Haemorrhagic cystitis was indicated after 48-72 hours by the production of heavily blood-stained urine in all animals. Formalin was instilled as in Groups I and Ia: 150 ml of 10 % solution in 5 dogs and 150 ml of 5 % Formalin in 5 dogs. The dogs were returned to the animal shelter and one dog of each group was killed 1, 2, 3, and 4 weeks after instillation and their bladders examined both macroscopically and histologically.

RESULTS

All bladders instilled with Formalin showed severely thickened walls with some oedema of the epithelium and a haemorrhagic exudate. Transmural inflammation, mucosal ulceration, and intense submucosal thickening and haemorrhage were evident microscopically. In addition, the cyclophosphamide-treated bladders showed the histological changes of cellular atypia, telangiectasia, and fibrosis of the detrusor muscle, similar to the findings previously described by Javadpour and Barakat (11). In all dogs with haemorrhagic cystitis the Formalin stopped the bleeding completely.

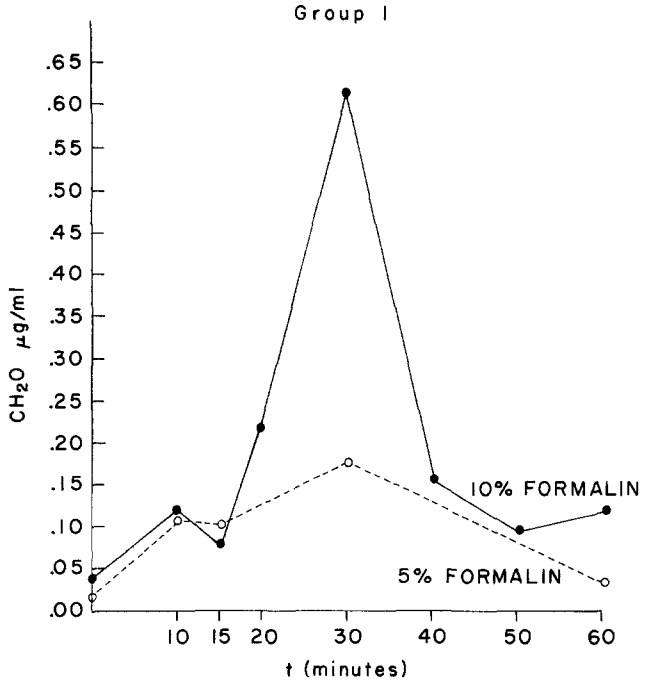

Fig. 1. Time-concentration study of the absorption of formaldehyde after intravesical instillation of 5 % and 10 % Formalin in 10 dogs with normal bladders (Group 1).

Progressively increasing amounts of formaldehyde, apparently related to the concentrations of Formalin introduced into the bladder, were found in the serum samples from all dogs in group I (Fig. 1). The peak concentration in the blood occurred at 30 minutes, corresponding with the period that Formalin was left in the urinary bladder. Peak serum levels using 5 % Formalin were 0.17 ± 0.17 µg/ml and for 10 % Formalin 0.61 ± 0.127 µg/ml. The levels gradually decreased after 30 minutes.

Higher serum levels were noted in the dogs in which haemorrhagic cystitis was induced with cyclophosphamide and the peak value occurred at 20 minutes. (Fig. 2). This may have resulted from the many open blood vessels demonstrated histologically. Visual examination of the bladder showed a considerably thickened wall, implying formaldehyde binding. This may explain the minimal formaldehyde recovery from the Formalin infusate and from the serum, which accounted for less than 0.1 % of the

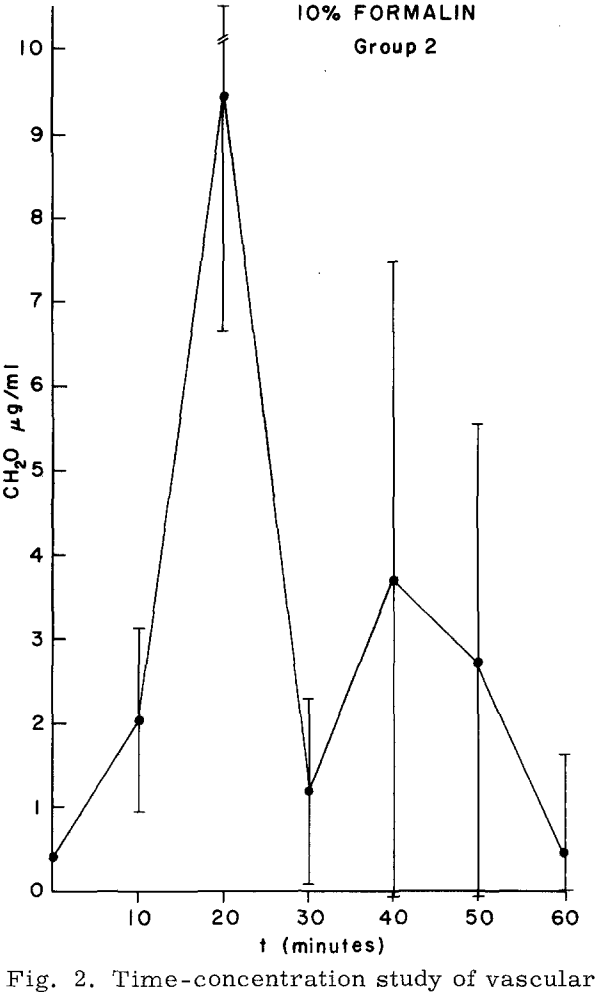

Fig. 2. Time-concentration study of vascular absorption of formaldehyde after intravesical instillation of 10 % Formalin in dogs with cyclophosphamide-induced haemorrhagic cystitis (Group 2).

orginal dry weight of formaldehyde in a 10 % or 5 % solution. Serial determinations up to 30 days after instillation demonstrate that formaldehyde is not only immediately absorbed through the urinary bladder of dogs but also bound and continuously released into the vascular system.

DISCUSSION

Cyclophosphamide is a cytotoxic bi-functional alkylating agent which has been used for several years in the chemotherapy of disseminated cancer, lymphoproliferative and myeloproliferative disorders, recently in cancer of the prostate (19), and in the nephrotic syndrome of childhood (2). Its wide margin of safety is probably attributable to a low general and organotropic toxicity, and particularly the less pronounced leucocyte toxicity (3). Yet, cyclophosphamide is unique among chemotherapeutic agents in that it may cause severe damage to the bladder. Indeed, urinary tract disorders with or without haemorrhagic cystitis are well-recognised complications of cyclophosphamide therapy, especially in children (5, 17).

Morphological and ultrastructural aspects of bladder damage following cyclophosphamide therapy as well as the mechanism of repair have been studied by several authors in a variety of animal species, mainly dogs and rats (4, 12, 13). The general pattern of bladder damage is described as one of early epithelial necrosis, followed by repair and hyperplasia of such magnitude that cyclophosphamide has been regarded as a potential bladder carcinogen (12). Recently Dale and Smith (7) reported on transitional carcinoma of the bladder associated with cyclophosphamide therapy in which they stressed the importance of bladder biopsies when dealing with cyclophosphamide-induced haemorrhagic cystitis. Although it is not known how much cyclophosphamide is required to produce neoplasia in man, several authors caution against the routine use of cyclophosphamide in various diseases (14). Metabolites of cyclophosphamide are largely excreted by the kidney and are probably responsible for the haemorrhagic cystitis which can be induced in dogs after injection of a single intravenous dose of cyclophosphamide 50 mg/kg (4).

Several authors (6, 10) have studied the penetration and vascular absorption of various agents such as nitrofurantoin, thiotepa, digoxin, sodium, and urea through the normal dog urinary bladder and have demonstrated continuous absorption. Schoenrock et al. (18) found that the absorption of kanamycin in dog urinary bladder is compatible with a passive diffusion system related to the concentration gradient. Rankin (16) stated that immediate systemic absorption of Formalin after intravesical instillation did not seem to be a problem, but the blood levels of Formalin were not determined in his study.

The present experimental study demonstrated and reproduced our clinical observations and measurements of transvesical vascular absorption of Formalin in patients treated for hemorrhagic cystitis. Whether this intravascular concentration is high enough to cause systemic damage cannot be determined. However, the findings reported here indicate that instillation of formaldehyde solution into the bladder is a simple and effective method of controlling bladder haemorrhage.

REFERENCES

1. Ascoli, R.: Mechanisch-chemische Stimulation der Harnblase bei neurogenen Blasenlähmungen. Zeitschrift für Urologie 63, 773 (1970)
2. Barratt, T. M., Bercowsky, A., Osofsky, S. G., Soothill, J. F.: Cyclophosphamide treatment in steroid-sensitive nephrotic syndrome of childhood. Lancet 1975 I, 55
3. Brock, N., Hohorst, H. J.: Metabolism of cyclophosphamide. Cancer (Philad.) 20, 900 (1967)
4. Chaves, E.: Cytotoxic effects of cyclophosphamide. An experimental study. Archivio italiano di pathologia e clinica dei tumori 10, 223 (1967)
5. Coggins, P. R., Ravdin, R. G., Eisman, S. H.: Clinical pharmacology and preliminary evaluation of Cytoxan (cyclophosphamide). Cancer Chemotherapy Reports 3, 9 (1959)
6. Conklin, J. D., Hollifield, R. D.: Studies on the movement of nitrofurantoin across the dog urinary bladder. Investigative Urology 5, 244 (1967)
7. Dale, G. A., Smith, R. B.: Transitional cell carcinoma of the bladder associated with cyclophosphamide. Journal of Urology 112, 603 (1974)
8. Fair, W. R.: Formalin in the treatment of massive bladder hemorrhage. Techniques, results, and complications. Urology 3, 573 (1974)
9. Frankel, S., Reitman, S., Sonnenwirth, A. C., (Eds.): Gradwohl's clinical laboratory methods and diagnosis. vol. 1, p. 306, 7th ed. St. Louis: C. V. Mosby Co. 1970
10. Gonzales, E. T., Glenn, J. F.: Experimental estimation of transvesical digoxin absorption. Investigative Urology 9, 238 (1971)
11. Javadpour, N., Barakat, H. A.: Bladder toxicity due to cyclophosphamide. Experimental induction and treatment. Urology 2, 634 (1973)
12. Koss, L. G.: A light and electron micros-

copic study of the effects of a single dose of cyclophosphamide on various organs in the rat. I. The urinary bladder. Laboratory Investigation 16, 44 (1967)
13. Locher, G. W., Cooper, E. H.: Repair of rat urinary bladder epithelium following injury by cyclophosphamide. Investigation Urology 8, 116 (1970)
14. Wood, L.: Cyclophosphamide and neoplasia. Lancet 1974 II, 898
15. Nicolaier, A.: Über die therapeutische Verwendung des Urotropin. Deutsche medizinische Wochenschrift
16. Rankin, K. N.: Intravesical formalin. Invest. Urol. 12, 150 (1974)
17. Rubin, J. S., Rubin, R. T.: Cyclophosphamide hemorrhagic cystitis. Journal of Urology 96, 313 (1966)
18. Schoenrock, G., Hari Kamat, M., Seebode, J. J.: Absorption of kanamycin from urinary bladder of the dog: A kinetic study. Surgical Forum 556 (1973)
19. Sinclair, G. R., Lupu, A. N., DeKernion, J. B.: Management of adenocarcinoma of prostate with diethylstilbestrol diphosphate and cyclophosphamide. Urology 5, 665 (1975)
20. Skinner, D. G.: Personal communication (1974)

Hans-Udo Eickenberg, M. D.
Section on Urology, Dept. of Surgery
Univ. of Louisville School of Medicine
Louisville, KY 40201, U.S.A.