

STUDIES ON THE PERMEABILITY OF DRUGS THROUGH VESICAL WALL

THE FIFTH REPORT : EXPERIENCES WITH INTRAVESICAL FORMALIN ADMINISTRATION

Nobuo KAWAMURA

From the Department of Urology, Tokai University, School of Medicine

(Director: Prof. N. Kawamura)

When some drug is injected into the bladder, it has been found to permeate through the bladder wall, and appear in the serum. Similarly, formaldehyde, which is in some clinical cases injected into the bladder on hemostatic purposes, could produce side effects if a large part of its injected dose is transferred into the serum. We, therefore measured the transfer of the agent into the serum in both experimental animals and human patients. Formaldehyde was found to be transferred into the serum through the bladder of rabbits with cystitis, but only a trace of it appeared in the serum through the normal bladder. The injection of 10 ml of a 10% solution of formaldehyde to rabbits with cystitis was followed by a peak level of 8 γ /ml in the serum. Judging from this level, the same amount injected to humans would not be high enough to cause any particular problems. In the actual study, the formaldehyde level in the serum of human patients was not detectable by the assay method used.

Key words: Formalin, Intravesical administration, Cystitis, Rabbit

INTRODUCTION

It is well documented that drugs introduced into the lumen of urinary bladder may be absorbed and be circulated. Instillation by catheter of thiotepa (Tespamin®) into the bladder for treatment or prevention of recurrence of vesical neoplasms has been reported to give rise to leukopenia and other adverse reactions, and later, certain drugs, notably antibiotics, have been described to diffuse and be circulated following their intravesical instillation. Diffusion of intravesically injected anticancer chemotherapeutic agents into the circulating plasma would pose problems in respect to adverse reactions and, accordingly, the dosage intervals and dose levels require investigation. If an antimicrobial agent with the property of being actively excreted in the urine is absorbed by the bladder, thus entering a cycle of diffusion into the tissues, the re-entrance into circulation and re-excretion into urine, thus may afford an

enhanced clinical benefit. The question thus arises of whether it is more advisable to increase fluid intake to increase the urine output or, otherwise, to restrict fluid intake so as to increase the intravesical drug concentration for improvement of pharmacodynamic efficiency.

In discussing transvesical diffusion of drugs, conditions of the bladder—whether it is inflamed, has neoplastic growths, or is intact—have bearing of no small concern; and, when viewed with respect to the drug to be instilled, such factors as drug concentration of solution, amount and pH of drug solution and molecular weight of the drug, have been shown to some extent to affect diffusion. Diffusion, in fact, varies with the type and, noticeably, with the instillation pressure as well, in the case of antibiotics and other drugs. Combination of drugs may also affect transvesical diffusion.

In urology, it has become a fairly widely applied practice in recent years to

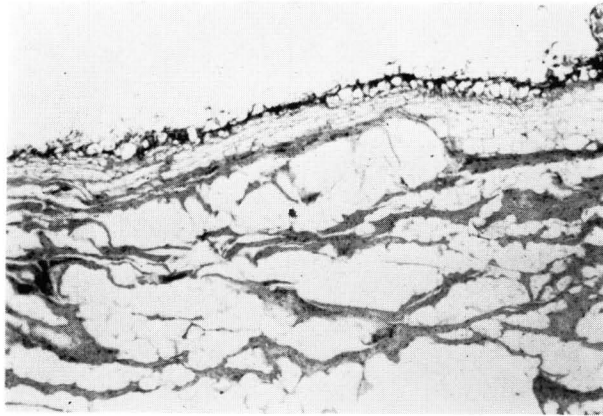


Fig. 1. Ether cystitis

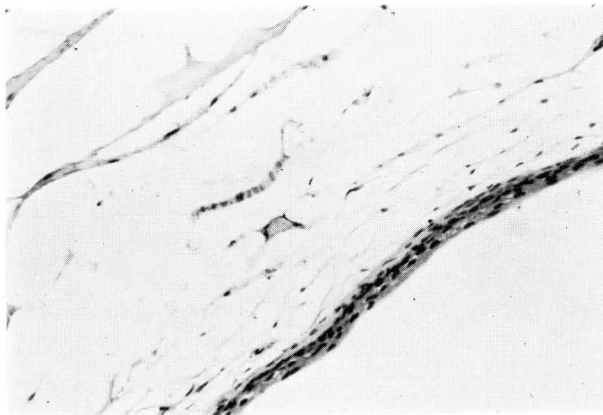


Fig. 2. Formalin cystitis

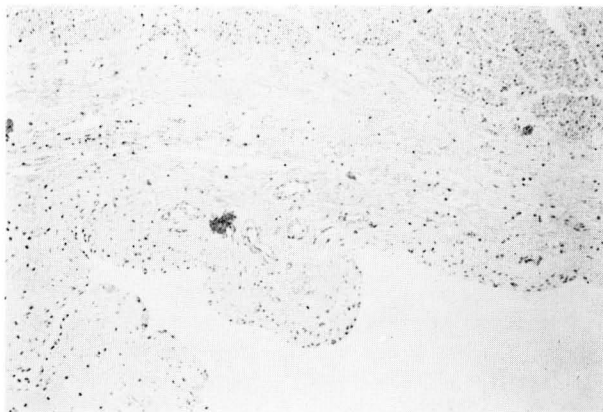


Fig. 3. Cyclophosphamide cystitis

inject formalin solution into the vesical lumen as a hemostatic approach mainly in cases of hard to control hemorrhage of the bladder by virtue of coagulating the mucosal protein. The bleeding urinary bladder naturally is inflamed and can readily be imagined to have an increased area of mucosal surface because of neoplastic growths. The purpose of this study was to determine what effects intravesical injection of formalin solution might exert on the bladder under such conditions and to ascertain whether and, if at all, to what extent the injected formaldehyde might become diffused into the circulation. The study also encompassed exploration of safety of the procedure and ascertainment of whether or not the urinary bladder physiologically permits diffusion of drugs introduced into the circulation intravesically.

METHODS

The following experimental procedure and methods of clinical investigation were employed:

Male adult Japanese albino rabbits were used. They were divided into groups subject to experimental induction of cystitis and normal control groups. For induction of cystitis, three different methods were used: 1) intravesical injection of ether, 2) intravesical injection of formalin, and 3) intravenous administration of cyclophosphamide.

1) Cystitis can be induced in rabbits by intravesical injection of 5 ml of ether.

With the rabbit restrained under pentobarbital anesthesia, ether was injected in a volume of 5 ml into the bladder via a urethral catheter. The injected ether vaporized by body temperature gradually went off through the catheter maintained in place, causing fairly severe cystitis medicamentosa (Fig. 1). The photomicrograph of the bladder 2 days after injection of ether showed extensive mucosal exfoliation, leaving only small areas of vesical wall intact.

2) Ten ml of 10% formalin solution J.P. was injected into the bladder through a urethral catheter as in the case of ether

injection, followed immediately by removal of the catheter. Figure 2 is a photomicrograph of the bladder 2 days after injection of 10% formalin.

3) Cyclophosphamide was made into a 20 ml physiological saline, solution 300 mg and injected via the auricular vein without anesthesia. A photomicrograph of the bladder from a rabbit injected 2 days previously with cyclophosphamide is presented in Figure 3.

These treatments to induce cystitis cast a considerable burden on the animal, causing deaths among some in all three treated groups even in the initial course of development of inflammation. The intravenous 300 mg caused noticeably high mortality, and survivors in the cyclophosphamide-treated group developed alopecia. Animals treated with ether or formalin almost always remained incontinent in urination.

Two days after the treatment of induce cystitis the urethra was recatheterized with a Foley catheter via which formalin solution was injected; each group was divided into two subgroups, one receiving 5 ml of a 5% formalin solution and the other 10 ml of a 10% formalin solution. The inlying Foley catheter was drawn out and a clamp placed on the shaft of penis so as to prevent outflow of the injected formalin solution. Serial blood samples were drawn from the auricular vein and, after separation of serum, assayed for formalin by the method of Nash (Table 1).

In the clinical study, attempts to obtain hemostasis were made using intravesical formalin injection on an elderly patient having terminal stage carcinoma of the bladder and one with carcinoma of the prostate with vesical infiltration, both showing persistent hemorrhage from extensive areas of tissues of the bladder. Five ml of 5% formalin solution J.P. was injected into the

Table 1. Composition of Nash's Reagent

Ammonium acetate	30.0g
Acetyl acetone	0.4ml
Aqua dil.	100 ml

bladder through a urethral catheter without anesthesia. On receiving the injection, the patients complained of slight irritation but neither described pain. Therefore, the injected fluid was allowed to remain in the bladder for 5 minutes and then drawn out by irrigation with physiological saline. Serum samples obtained at various times after irrigation were assayed for formalin using Nash's procedure. A satisfactory hemostatic effect was observed in the patients studied.

RESULTS

The results of formaldehyde assays on serial serum specimens obtained from nor-

mal rabbits following intravesical injection of 10 ml of 10% formalin solution J.P. are presented in Table 2, where t denotes a trace quantity. As is shown in the Table, there was no appreciable rise in serum formaldehyde concentration even when the injected formalin remained in the bladder for 3 hours.

Figure 4 shows data from rabbits with induced vesical inflammation and injected with 10 ml of 10% formalin solution. In the animals with formalin-induced cystitis, the serum formaldehyde content increased rapidly to as high as 5 γ /ml in 15 minutes after formalin injection, then dropped after 60 minutes, to virtually zero at 180 minutes. In rabbits with cystitis induced by injection

Table 2. Intravesical injection of formalin in normal bladder of rabbits (10% formalin 10 ml)

No of rabbit	10'	15'	20'	30'	40'	45'	50'	60'	90'	120'	180'
1	t		0	t	t		10	t			
2	t	0		t		t		t		t	t
3	0	0		t				t		t	t
4	0			t				t	t	t	t
5	0							0		0	

t=trace

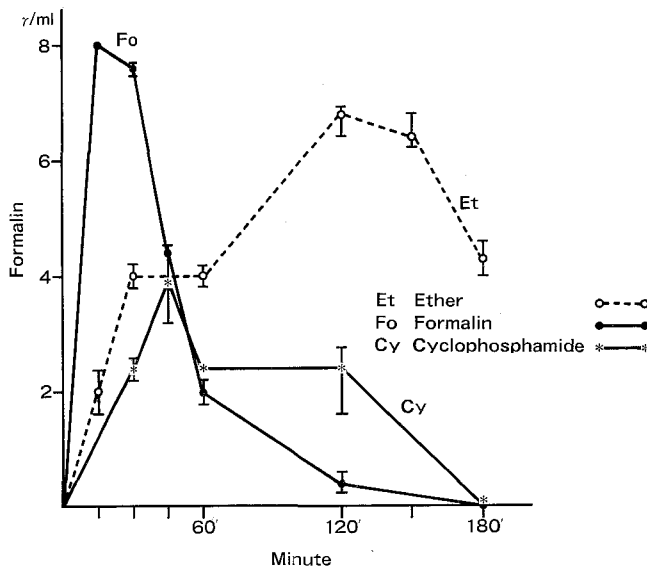


Fig. 4. Intravesical injection of formalin in cystitis bladder of rabbits (10%, 10 ml)

Table 3. Intravesical injection of formalin in normal bladder of rabbits (5% formalin 5 ml)

No. of rabbit	10'	20'	30'	40'	50'	60'	90'	120'
1	0	0	t	t	t	t	0	0
2	0	0	t	t	t	t	0	0
3	t		t			t	0	t
4	t	t				3.0	1.2	t

t=trace

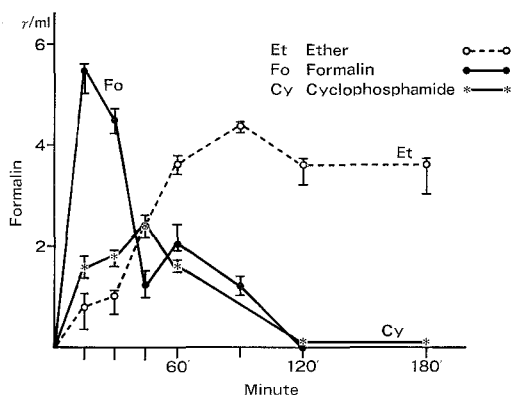


Fig. 5. Intravesical injection of formalin in cystitis bladder of rabbits (5%, 5 ml)

Table 4. Intravesical injection of formalin to bladder tumor patients (5% formalin 10 ml)

pts.	30'	60'	120'
M	0	0	0
N	0	0	0

of ether, on the other hand, serum formaldehyde reached its peak concentration at 120 minutes after intravesical formalin injection, thus generally delayed as compared with that in the animals with formalin-induced cystitis. A less conspicuous rise of serum formaldehyde occurred, with a maximum value of 4 γ /ml in the rabbits in which vesical inflammation had been evoked by cyclophosphamide. Their serum formaldehyde levels at 120 minutes after formalin injection were still relatively high, compared

to the peak value.

Table 3 shows the serum formaldehyde levels in normal rabbits following intravesical injection of 5 ml of 5% formalin solution. Occasionally, it rose to 3.0 mcg/ml within 60 minutes after formalin injection, though the concentration fell noticeably within 90 minutes. This finding is noteworthy in that it implicates that formalin introduced into the bladder does not enter the blood circulation.

Fig. 5 shows the data from the subgroups of rabbits with induced inflammation of the bladder and injected intravesically with 5 ml of 5% formalin solution. As was the case with 10 ml of 10% formalin solution, the serum formaldehyde concentration reached its peak 15–30 minutes after injection in the rabbits with formalin induced cystitis, whereas it reached a plateau 60 minutes after injection in those with ether-induced cystitis. The animals with cystitis induced by cyclophosphamide showed a peak serum formaldehyde value at 45 minutes after formalin injection.

Neither patient clinically receiving intravesical formalin injection for hemostasis showed any demonstrable amount of serum formaldehyde during the examined period of 120 minutes after formalin injection (Table 4).

COMMENT

There exists an increasing trend of widespread application of intravesical injection of formalin as a means to control bleeding from the urinary bladder. However, how safe is this hemostatic approach?

Occurrence of formaldehyde at high concentrations in the blood is known to lead to hepatic and renal damage and neurological manifestations of the CNS. Clinically, flare of the skin and delirious adverse reactions have also been reported for formaldehyde intoxication. Diffusion of an intravesically introduced drug into the circulation, nevertheless, seems to vary with the condition of the patient, i.e. degree of inflammation of the bladder, intravesical dose of the agent, injection pressure, pH of solution to be injected, and type of the agent.

Our previous study demonstrated that the pH of the drug solution had no significant influence, and that the volume of drug solution had no appreciable effect as long as it did not exceed 20 ml in the case of rabbits.²⁾

On these grounds, we investigated the degree of serum formaldehyde increase in animals and patients following intravesical introduction of formalin solution. There was little or no diffusion of formalin through the normal urinary bladder into the circulation, irrespective of formaldehyde concentration in the solution. It was also noted that, in experimentally induced cystitis, the time-course of diffusion into circulating plasma varied in pattern with the mode by which vesical inflammation was induced. This might be due to differences in the characteristics of the cystitis induced, though further experiments with different drugs for intravesical infusion need to be done to ascertain it.

We do not know which of the 3 types of cystitis induced experimentally in rabbits, resembles hemorrhagic cystitis or cystitis associated with tumor of the bladder in man. The induced inflammations of the bladder in rabbits were remarkably severe and it may be said that cystitis of such gravity scarcely occurs in humans. It would follow that the serum formaldehyde concentrations observed in these animals are nearly maximal from the practical viewpoint.

Clinically, no detectable concentration of formaldehyde was found in the serum as determined by the Nash method after

intravesical injection of formalin solution, in the apparent presence of inflammation of the bladder. This would be attributed to the fact that they received injection of formalin in practically the same quantity as that given experimentally to rabbits despite their body weight and amount of body fluid being approximately 20-fold, compared to the rabbit; hence about 1/20 of the highest dose injected into the bladder of rabbits. Accordingly, it cannot be said that the urinary bladder of patients was virtually normal merely because the patients showed serum values for formaldehyde diffusion from bladder comparable to those observed in rabbits with normal bladder.

Is formalin liable to be readily diffused into the circulation when introduced into the bladder? It is known from other series of experiments that the rate of drug diffusion into the circulation varies considerably with the drug after its introduction into the vesical lumen. No comparison can be made, nevertheless, with formalin in this respect because neither formaline nor its related compounds have been assessed as yet. It seems probable that formaldehyde is moderately diffused into the circulation.

The variations in maximal drug diffusion into the circulation seen among the three variously treated groups may be attributed to such factors as difference in severity of cystitis produced and that in morphologic characteristics of the cystitis. Such variations have been reported with other drugs as well.^{3,4)}

How can the differences in pattern of time-course of injected formaldehyde diffusion be explained, then? It is yet to be ascertained, however, whether the susceptibility of the vesical tissue is under the influence of intravesical pressure which may vary with the type of cystitis.

It has been reported by other investigators that intravesically introduced drugs are well absorbed from an inflamed bladder while absorption is minimal when the bladder is intact.^{8,9)} The present data obtained with formalin solutions support these findings. However, our past experience⁵⁻⁷⁾ has shown that such differences between

inflamed and intact urinary bladders exist with certain drugs but not with certain other drugs. It cannot be sweepingly said, therefore, that inflamed bladders permit drug diffusion into the circulation and intact bladders do not. Intravesical injection of formalin solutions into the intact bladder is expected to have immediately caused chemical irritation with consequent development of inflammation, thereby permitting good absorption of formaldehyde into the circulation, in the present series. Yet, there was no appreciable difference in absorption.

CONCLUSIONS

Experimental and clinical studies were performed to assess diffusion of intravesically injected formalin solutions into the circulation, with the results leading to the following conclusions:

1. Intact urinary bladders permitted little or no diffusion of formaldehyde into the circulating serum.

2. Formalin solutions introduced into the lumen of inflamed urinary bladders entered the circulation, and the time-course of formaldehyde diffusion into serum varied in pattern with the mode by which cystitis was induced.

3. The amount of formaldehyde diffused into the circulation did not correlate with the volume or concentration of formalin solutions injected into the bladder.

REFERENCES

- 1) Cole DR, Howley T, Roman R, Dreyer B, Tan YL, Gonzales E and Rousselot LM: Absorption and activity studies on intraluminal thio-tepa in the dog's bladder. *J UROL* **94**: 556~558, 1965
- 2) Conklin JD and Hollifield RD: Studies on the movement of nitrofurantoin across the dog urinary bladder. *Inv Urol* **5**: 244~249, 1967
- 3) Adachi T: Transport of Antibacterial drugs into the canine bladder wall: Its significance in evaluation of antibacterial drugs in urine for the treatment of Urinary Tract Infection. *Jap J Urol* **62**: 220~228, 1971
- 4) Tohma H and Emoto K: Experience of the local treatment with endoscopic application of Polimixin B-solution in the clinical urology. *Nishinohon J Urol* **33**: 705~709, 1971
- 5) Chamberlain G and Needham P: The absorption of antibiotics from the bladder. *J Urol* **116**: 172~173, 1976
- 6) Kiriya T: Drug permeability of the bladder wall.: Experimental aspects of chemotherapy for the defunctionalized bladder. *Nishinohon J Urol* **39**: 14~24, 1977
- 7) Kawamura N: Studies on the permeability of drugs through vesical wall: The first report. *Nishinohon J Urol* **42**: 45~48, 1980
- 8) Brown RB: Experiences with intravesical formalin administration in advanced carcinoma of the bladder. *Brit J Urol* **42**: 738~739, 1970
- 9) Eickenberg H-U and Adcock R: Vascular absorption of intravesical formalin in cyclophosphamide induced haemorrhagic cystitis. *Urol Res* **4**: 5~8, 1976
- 10) Kawamura N: Studies on the drug permeability of vesical walls. The absorption of sulbenicillin from the bladder. *Jap J Antibiot* **614**~623, 1979
- 11) Kawamura N: Permeability of adriamycin through vesical walls and its instillation therapy. *Tokai J Exp Clin Med* **4**: 283~290, 1979 (Accepted for publication, April 18, 1983)

和文抄録

薬剤の膀胱壁透過性に関する研究

第5報：ホルマリンの膀胱腔内注入について

東海大学医学部泌尿器科学教室（主任：河村信夫教授）

河 村 信 夫

膀胱内に注入したホルマリンについて、その血清への移行を検討し、次のごとき結論を得た。

ウサギ正常膀胱からはホルマリンは血清にほとんど移行しない。薬物により膀胱炎を起させたウサギの膀胱に、ホルマリンを注入すると血清中に移行するが、その移行のしかたは膀胱炎の起し方により異なる。ま

た移行するホルマリンの量は、注入したホルマリンの量や濃度と平行しない。

本研究の費用の一部は1979年および1980年度の文部省科学研究費（B）No. 448309 によった。

本研究の内容は第9回国際泌尿器科学会、（サンフランシスコ1982年）において発表した。