STUDIES ON THE DRUG PERMEABILITY OF VESICAL WALLS

II. THE ABSorption OF SULBENICILLIN FROM THE BLADDER

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The present series of experimental studies was undertaken to give solutions to the following questions: (1) can antibiotics administered intravesically be absorbed from the wall of the bladder?, (2) if so, does their intravesical injection prove to be effective in the treatment of cystitis? and (3) if this true, can their intravesical injection provide an advantage over their systemic use since a larger dose can be given at a higher concentration by the former method of administration?

If an antibiotic is transferred in a substantial amount to the blood following its intravesical administration, the end result of such medication may be identical with that of administration by systemic routes since the antibiotic transferred into the circulation will eventually be recovered in the urine after being excreted by the kidney or through the wall of the bladder. It may be said, then, that a large intravenous or intramuscular dose can be used more advantageously than cumbersome, frequent intravesical doses, although this may not always be true with all types of antibiotics. If, on the other hand, an intravesically administered antibiotic is not transferred to the blood in substantial quantities or is promptly eliminated from the circulation after being transferred to it and, moreover, proves to be comparable to its systemic administration in terms of therapeutic efficacy against infection, this particular mode of antibiotic therapy may be suited for the treatment of patients with hepatic and/or renal impairment, those in whom injection is impractical as well as pregnant women.

These considerations led us to conduct basic and clinical studies of sulbenicillin (SBPC) in order to determine whether this antibiotic can permeate into the blood or can pass through bladder walls following intravesical injection, to what extent it is recovered in urine and whether or not it is clinically effective.

Material and Methods

The concentrations of SBPC in the serum, tissues and urine invariably were determined by bioassay using Pseudomonas aeruginosa NCTC as the test organism and the standard cup method of the Japan Chemotherapy Association.

Basic Study

SBPC was investigated for its transfer to the serum following intravesical injection in rats and rabbits.

1 Experiment in Rats

Our previous experiment (to be published elsewhere) demonstrated that, while the amount of a fluid absorbed from the vesical wall following its intravesical injection in a dose of more
than 0.5 ml increases with an increasing dose of injection, its amount absorbed following an intravesical dose of less than 0.5 ml remains constant irrespective of the amount injected. In view of this finding SBPC was injected intravesically in normal rats as well as rats with cystitis at 3 doses of 300 mg, 24 mg and 12~15 mg, but invariably as a solution in 0.5 ml physiological saline in this experiment.

Cystitis was induced in the rats by the following procedure: upon laparotomizing the animals under ether anesthesia ca. 0.5 ml of 10% formalin was injected into the vesical lumen with a thin syringe needle piercing the bladder at its vertex; the hole bored by the needle was closed by ligation. Two days later the animals with chemical cystitis thus induced were used for the experiment.

The intravesical injection of SBPC was performed with the animals laparotomized under ether anesthesia and subjected to ligation of both ureters and penis, in otherwise the same manner as in the case of the injection of formalin. The anesthesia was maintained for about 10 minutes after the injection of SBPC.

The group of rats injected with 300 mg/0.5 ml of SBPC consisted of 2 subgroups, i.e., 8 normal rats and 8 rats with cystitis. Two animals each from the subgroups were sacrificed 30 minutes, 1, 2 and 4 hours after the injection of SBPC and determined for concentrations of the drug in the serum and the vesical wall. Blood samples invariably were taken by cardiocentesis. The bladder was totally resected by cutting its neck, its fluid contents were removed and then, after being washed once, the excised organ was weighed. Subsequently the bladder tissue was prepared as an emulsion which was assayed for SBPC. As can be seen in Fig. 1, the normal rats gave a maximum serum SBPC level of 875 μg/ml (mean), while the serum level of SBPC in the rats with cystitis attained a maximum of 1,210 μg/ml at 30 minutes after intravesical injection but thereafter did not show any consistent tendency. These findings suggest that SBPC might be eliminated by way of some alternative organs, e.g. the liver, when its urinary excretion is artificially blocked.

The results of SBPC assay in the group injected with 24 mg/0.5 ml were as illustrated in Fig. 2. This group comprised 10 normal rats and 6 rats with cystitis. These animals were sacrificed sequentially in the same manner as in the preceding group. From the figure it becomes obvious that the SBPC contents of the serum and bladder tissue were higher at 1 hour than at 30 minutes after intravesical injection and thereafter diminished gradually.

Fig. 3 represents those animals receiving 12~15 mg/0.5 ml of SBPC intravesically. The observed discrepancies in the injected
dose of SBPC are due to technical errors incidental to dilution of the drug. Even with measurement errors taken into account, the intravesical dose departed from the range of 12~15 mg in no instances. This group consisted of 12 normal rats and 12 rats affected with cystitis. With this lowest intravesical dose of SBPC, measurements of the tissue levels of the drug yielded essentially the same findings as in the preceding experiment. In addition it was demonstrated that the serum and bladder tissue levels of SBPC become heightened with increasing intravesical dose.

2. Experiment in Rabbits

The use of rabbits permits experimentation with a larger amount of medicated fluid injected intravesically without resorting to anesthesia and, moreover, allows repeated collection of blood from the same individual. For these reasons rabbits were employed in another experiment.
Our previous basic experiment showed that in this animal species the effect of the pressure of intravesical injection on drug absorption from the wall of the bladder is negligible as long as the volume of fluid injected does not exceed 5 ml.

Either the day previous to the experiment or 2 days before the subject rabbits had their ureters transplanted into the skin under anesthesia. The distal cut ends of the ureters were ligated. The intravesical injection of SBPC was made after the bladder was emptied by urethral catheterization. The penis was ligated after injection of the drug. Blood samples were taken serially from the auricular vein.

Five rabbits were employed. Following the intravesical injection of 1 g SBPC tissue levels of the drug showed a similar patterns of change and were still increasing at 4 hours in all animals. These results are not consistent with those obtained in rats, but the reason for this is not known. Four days after the intravesical dose the tissue levels of the drug declined.

Clinical Study

As the basic experiments demonstrated the safety for human use of intravesically injected SBPC, the drug was administered by the same route to 11 female patients with acute, simple cystitis and investigated for its therapeutic efficacy, serum levels and recovery in the urine.

The drug (SBPC) was used at a dosage of 5 g dissolved in 20 ml physiologic saline initially, then at a dosage of 1 g given as a solution in 20 ml physiologic saline. Since, however, these doses were irritant enough to the acutely inflamed bladder to cause pain and prompt micturition, the dosage was changed to 1 g dissolved in 100 ml physiologic saline, which was injected into the bladder through a catheter. One hour thereafter blood and urine samples were collected for measurement of the concentration of SBPC.

Of the 11 patients, 3 received 5 g of SBPC dissolved in 20 ml of physiologic saline while the other 8 were given 1 g of SBPC as a solution in 100 ml physiologic saline. In 7 of these 11 patients the drug concentration in the serum and urine at 1 hour after intravesical injection was measured.

The blood level of SBPC following intravesical injection of 5 g was found to be 2.6 μg/ml in one (only) case. Blood levels of the drug yielded by 1 g injected intravesically, on the other hand, varied widely, being less than 0.5 μg/ml in 3 cases but 3.6 μg/ml at the maximum. The fraction of the intravesical dose recovered in urine also was quite variable, ranging from 95.2% to 38.9%. The urinary concentration of the drug varied to a considerable extent as it depends partly on the urine volume.

The clinical efficacy of intravesically injected SBPC was assessed according to the UTI criteria. As a rule, no antibiotic medication was given after the intravesical injection of the test drug. Three days after the test medication another examination of the urine was made and the results were compared with those obtained before medication. Responses to intravesically injected SBPC were rated as excellent in 2 cases, good in 3 cases and poor in 3 cases, the remaining 3 cases being unassessable.

From these results it may safely be said that 1-hour intravesical retention of a fluid containing 10,000 μg/ml of SBPC alone will prove fairly effective in the control of acute cystitis. In a previous study the blood and urine levels of the antibiotic following the intravenous drip infusion of 5 g of SBPC over 2 hours were reported to be around 210 μg/ml (maximum attained at 2 hours) and 10.2 mg/ml, respectively. Thus, the urine and serum levels of SBPC obtained
Table 1. Efficacy of intravesical infusion therapy of SBPC against acute cystitis

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Dose</th>
<th>Detected bacteria</th>
<th>Sensit. to SBPC</th>
<th>WBC in urine</th>
<th>Miction pain</th>
<th>Efficacy</th>
<th>Serum levels</th>
<th>Urinary levels</th>
<th>Recovery from urine (%)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K.M.</td>
<td>5 g</td>
<td>Before E. coli</td>
<td>(-) 10~15 (-)</td>
<td>(-) (+)</td>
<td>(-) (++)</td>
<td>Markedly effective</td>
<td>2.6 µg/ml (1 hr.)</td>
<td>24,400 µg/ml</td>
<td>63.4</td>
<td>Joint administration of other antibiotics</td>
</tr>
<tr>
<td>2</td>
<td>S.S.</td>
<td>5 g</td>
<td>St. epidermidis</td>
<td>(-) (+) (+)</td>
<td>(-) (+)</td>
<td>(-) (++)</td>
<td>Poorly effective</td>
<td>2.6 µg/ml (1 hr.)</td>
<td>24,400 µg/ml</td>
<td>63.4</td>
<td>Joint administration of other antibiotics</td>
</tr>
<tr>
<td>3</td>
<td>K.M.</td>
<td>5 g</td>
<td>Before E. coli</td>
<td>(-) (++) (-)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Unavailable</td>
<td>2.6 µg/ml (1 hr.)</td>
<td>24,400 µg/ml</td>
<td>63.4</td>
<td>Joint administration of other antibiotics</td>
</tr>
<tr>
<td>4</td>
<td>S.S.</td>
<td>1 g</td>
<td>Before E. coli α-Strept.</td>
<td>(+) (-) (-)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Markedly effective</td>
<td>Less than 0.5 µg/ml (1 hr.)</td>
<td>3,700 µg/ml</td>
<td>38.85</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>K.Y.</td>
<td>1 g</td>
<td>Before E. coli</td>
<td>(+) (++) (+)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Moderately effective</td>
<td>3.6 µg/ml (1 hr.)</td>
<td>6,800 µg/ml</td>
<td>95.2</td>
<td>In pregnancy</td>
</tr>
<tr>
<td>6</td>
<td>S.M.</td>
<td>1 g</td>
<td>Before E. coli</td>
<td>(-) (+) (+)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Moderately effective</td>
<td>Less than 0.5 µg/ml (1 hr.)</td>
<td>3,700 µg/ml</td>
<td>38.9</td>
<td>In pregnancy</td>
</tr>
<tr>
<td>7</td>
<td>Y.H.</td>
<td>1 g</td>
<td>Before E. coli</td>
<td>(-) (++) (+)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Moderately effective</td>
<td>Less than 0.5 µg/ml (1 hr.)</td>
<td>3,700 µg/ml</td>
<td>38.9</td>
<td>In pregnancy</td>
</tr>
<tr>
<td>8</td>
<td>S.K.</td>
<td>1 g</td>
<td>Before E. coli</td>
<td>(-) (++) (+)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Poorly effective</td>
<td>Less than 1.0 µg/ml (1 hr.)</td>
<td>5,200 µg/ml</td>
<td>65.0</td>
<td>In pregnancy</td>
</tr>
<tr>
<td>9</td>
<td>F.H.</td>
<td>1 g</td>
<td>Before E. coli</td>
<td>(+) (++) (+)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Poorly effective</td>
<td>Less than 1.0 µg/ml (1 hr.)</td>
<td>3,200 µg/ml</td>
<td>44.8</td>
<td>In pregnancy</td>
</tr>
<tr>
<td>10</td>
<td>A.T.</td>
<td>1 g</td>
<td>Before Negative</td>
<td>(+) (++) (+)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Unavailable</td>
<td>Less than 0.5 µg/ml (1 hr.)</td>
<td>2,800 µg/ml</td>
<td>51.8</td>
<td>In pregnancy</td>
</tr>
<tr>
<td>11</td>
<td>S.K.</td>
<td>1 g</td>
<td>Before Negative</td>
<td>(++) (++) (+)</td>
<td>(-) (++)</td>
<td>(-) (++)</td>
<td>Unavailable</td>
<td>Less than 0.5 µg/ml (1 hr.)</td>
<td>4,700 µg/ml</td>
<td>46.6</td>
<td>In pregnancy</td>
</tr>
</tbody>
</table>
Table 2. Transfer of SBPC into serum and vesical wall after its intravesical infusion

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Dose (g)</th>
<th>30 min. (mg/ml)</th>
<th>60 min. (mg/ml)</th>
<th>Time (min)</th>
<th>Urinary bladder Concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Y.H.</td>
<td>5</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
<td>8,000</td>
<td>86.0</td>
</tr>
<tr>
<td>2</td>
<td>H.T.</td>
<td>5</td>
<td>&lt;1.0</td>
<td>4.5</td>
<td>14,000</td>
<td>24.0</td>
</tr>
<tr>
<td>3</td>
<td>K.H.</td>
<td>5</td>
<td>&lt;1.0</td>
<td></td>
<td></td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>4</td>
<td>H.H.</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>5</td>
<td>T.S.</td>
<td>2</td>
<td>&lt;1.0</td>
<td></td>
<td>30</td>
<td>96.0</td>
</tr>
<tr>
<td>6</td>
<td>K.T.</td>
<td>1</td>
<td>&lt;0.5</td>
<td></td>
<td>30</td>
<td>9.6</td>
</tr>
<tr>
<td>7</td>
<td>T.T.</td>
<td>1</td>
<td>&lt;0.5</td>
<td></td>
<td></td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>8</td>
<td>O.K.</td>
<td>1</td>
<td></td>
<td></td>
<td>70</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>9</td>
<td>K.T.</td>
<td>1</td>
<td>&lt;1.0</td>
<td></td>
<td>30</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>10</td>
<td>T.M.</td>
<td>1</td>
<td>&lt;1.0</td>
<td></td>
<td>110</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>11</td>
<td>E.K.</td>
<td>1</td>
<td>&lt;1.0</td>
<td></td>
<td>120</td>
<td>&lt;2.0</td>
</tr>
</tbody>
</table>

by us after intravesical injection were the same test times and 1/100, respectively, of the corresponding values observed after intravenous infusion in the study described above. However, a still larger amount of SBPC may actually be absorbed from the wall of the bladder and subsequently excreted directly into the vesical lumen or through the kidney.

It should be noted that of 6 cases in which the infecting organism was demonstrated to be insensitive to SBPC, the therapeutic result was rated as good in 3 and as poor in 2 (the remaining 1 being unassessable), a finding suggesting that the intravesical injection of SBPC in large doses might prove effective even against unsusceptible organisms.

Of 8 cases of E. coli infection, 2 were rated as showing an excellent response, 2 good response and 2 poor response, while one case of infection with St. epidermidis was categorized as having a poor response. The intravesical injection of SBPC produced irritation that was severe enough to necessitate micturition in 10 minutes in one (Case No. 3) of these 11 cases. In 4 others vesical irritation occurred only to the extent that the patients was able to endure the desire to void for one hour. No adverse side-effects were otherwise encountered.

In a subsequent experiment determination was made of the extent to which SBPC is transferred to the blood, urine and bladder tissue following a prophylactic intravesical dose (as a solution in physiologic saline) for the prevention of infection at surgery upon the bladder. The dose was 5 g/100 ml in 4 cases, 2 g/100 ml in 1 case and 1 g/100 ml in 6 cases, the medication being given under anesthesia in all instances. The blood level of SBPC did not exceed 1.5 μg/ml at 30 minutes in any case, but in some cases it amounted to 4.5 μg/ml in 1 hour. In other cases pertinent blood samples could not be obtained for surgical reasons. The blood and urine levels of SBPC following its injection into a partially resected bladder were also determined in 9 and 3 cases, respectively, though at varying intervals after dosing. These results indicated that these tissue levels of the drug may change depending upon the drug concentration administered.

Discussion

For a long while it has been known that a drug injected into the vesical lumen in absorbed
from the wall of the organ and eventually is transferred into the systemic circulation. This phenomenon allegedly is affected by the pH, concentration and molecular weight of the drug as well as by its volume of injection4,5) but dose not seem to be accounted for by active permeation.

The absorption of antibiotics from the bladder has been the subject of excellent studies by KIRIYAMA4), ADACHI5), MITA7) and CHAMBERLAIN and NEEDHAM8). Reports are already available on the study of penicillin (PC), streptomycin (SM), sulfamethoxazole-trimethoprim (ST), nitrofurazone (NF), tetracyclin (TC) and colistin (CL) as well as a variety of anticancer drugs.

All these studies concern the physiology of the bladder but are also related, in some way, to an innovation of the method of use of antibiotics. If an antibiotic is transferred in a substantial amount to the wall of the bladder or serum after it is excreted in the urine, it would be more advantageous that the patient fill his bladder maximally after being administered with the drug. By the same token, in the presence of cystitis a therapeutic advantage will be afforded by elevating the concentration of an antibiotic in the urine through reduction in water intake and also by elevating the intravesical pressure by decreasing the frequency of urination and thereby prolonging the duration of contact of the drug with the wall of the bladder.

From the viewpoint of side-effects antibiotic therapy should be given at the minimum necessary dose in the treatment of urinary tract infection. This particular dose of antibiotic is customarily determined on the basis of the MIC and the urinary, as well as serum levels of that antibiotic. However, the relative therapeutic importance of these factors still remains to be clarified.

MITA7) has reported a detailed study on the clinical implications of the urine level of antibiotics. His experiment was conducted with cephaloridine (CER) in dogs and led him to conclude that CER found in the urine mainly was derived from the kidney, with only a small fraction coming from the bladder, and that the antibiotic excreted in the urine permeates through the vesical mucosa again to be transferred to tissues of the whole body.

NISHIMURA and KAWAMURA9) reported, in 1968, that sulfamethizole was transferred into vesical tissues after its intravesical injection in dogs and its rate of transfer into the bladder increased in the presence of formalin-induced cystitis. In the study of the permeability of tissues to TC, CL and SM in the dog, ADACHI6) in 1972 investigated the transfer of these drugs into the urine, blood and vesical tissue reporting that the three substances, when injected intravesically, are all transferred into the vesical tissue and thence to the blood and the urine, their transfer into the vesical tissue is affected little by the pH or osmotic pressure of the injected fluid and occurs to a greater degree in the presence of organ inflammation. Ether was used for the production of inflammation.

It has been established by PUST et al.11) that formalin is capable of inducing cystitis in experimental animals. Since, however, EICHEMBERG and ADCOCK10) recognized that in the presence of cystitis formalin itself can be absorbed from the wall of the bladder, errors due to the bactericidal action of formalin are very likely to occur in the measurement of antibiotic concentrations in the blood and tissues immediately after formalin-induced cystitis. Moreover, when formalin is used in large quantities, its absorbed fraction may prove fatal to animals. Accordingly, we employed rats for the experiment after an interval of 2 days following the intravesical injection of formalin. Similarly, rabbits were appropriated for the experiment after washing of the bladder with as much physiologic saline as possible and a subsequent 2-day interval following treatment with formalin.

Other reported studies on the absorption of antibiotics include those on the transfer of PC and SM and of NF by NAKAHIRA11) and CONKLIN19), respectively. These studies affirm the absorption of antibiotics from the bladder. KIRIYAMA3) investigated the permeability of rat's bladder to SBPC, cefradine (CED), dibekacin (DKB), gentamicin (GM), TC, chloramphenicol (CP), rifampicin (RFP) and nalidixic acid (NA) and also made reference to their clinical use. In both rats and humans these antibiotics were demonstrated to permeate the bladder wall. He also surmised that ampicillin (ABPC) and its related compounds might be transferred to the circulating blood by way of the lymphatic system.

As for the antibiotic in our present study, SBPC, KIRIYAMA4) carried out an experiment
using it in bilaterally nephrectomized rats. According to this author, SBPC disappeared from
the circulation within 24 hours after a single intravesical dose. However, the antibiotic activity
in the fluid contents of the bladder was appreciably high at 6 hours after dosing and was still
detectable even at 24 hours after dosing and was still detectable even at 24 hours if micturition
was not allowed to occur during this time interval; thus the patterns of change in the antibiotic
activity of the fluid contents of the bladder was nearly identical to that observed with ABPC.
He mentioned further that following the intravesical injection of cefazolin (CEZ) the antibiotic
activity in blood persisted for a long while even though the fluid contents of the bladder quickly
lost much of their antibiotic activity.

The reason why we chose SBPC as the drug for the present study is three-fold:

1. As shown previously by OHKOSHI et al.3), this antibiotic is used in massive intravesical
doses in occasional cases. It is not certain whether the urine level of the antibiotic yielded by
such a dose should be considered as representing the totality of the fraction excreted by
the kidneys or the remainder thereof that has escaped from being reabsorbed from the wall
of the bladder. Thus the possibility exists that SBPC is present at higher concentrations in
pelvic or ureteric urine than in vesical urine

2. SBPC has a relatively broad spectrum of antimicrobial activity and is reasonably free
from serious side-effects except for shock. Therefore, if the drug is transferred into the vesical
wall in a larger amount and in a smaller amount to the serum, its intravesical injection would
provide a safe means of treating, for example, acute cystitis during pregnancy.

3. Being lower in molecular weight than many other recently developed antibiotics, SBPC
is expected to have a higher tissue penetrability.

In the present experiment in rats SBPC was injected intravesically at a concentration of
24~600 mg/ml, levels that are much higher than a urine level of 10.2 mg/ml achieved with
5 g of SBPC administered by intravenous drip infusion in humans. In rabbits the drug was
administered intravesically at a concentration of 1 g/5 ml (or 200 mg/ml), which exceeds urine
levels of the drug yielded by the intravenous drip infusion of 5 g. According to NAKAGAWA13),
the highest urine levels of SBPC attained 0~2 hours after the intravenous injection of 2, 5
and 10 g (drip infusion) were approximately 15, 230 and 100 mg/ml, respectively. On the basis
of these figures and also on the analogy of urine levels expected to result from an intravenous
dose of 20~30 g the concentrations at which to inject the drug intravesically were set at 24,
48 and 600 mg/ml as mentioned earlier. The human intravesical dose of the drug, on the other
hand, was set at 1 g/100 (10 mg/ml) or above. This was because at this concentration level
the drug may reasonably anticipated to prove effective against most of organisms likely to infect
the bladder, since, according to OKADA14), organisms that were resistant to above 1.6 mg/ml of
SBPC accounted for 36.3%, 3.7% and 3.3%, respectively, of infections with Citrobacter, Pseu-
domonas aeruginosa and Serratia.

Turning to the amount of the antibiotic transferred into the wall of the bladder, our data
indicate that maximum SBPC concentrations attained in the human bladder tissue with 1, 2
and 5 g injected intravesically were less than 9.6 µg/g, 96.0 µg/g and 86.0 µg/g, respectively.
Animal experiments have shown greater variations in the drug concentration in bladder tissue
with different individuals than in humans, some rats having demonstrated as high a value as
above 1,000 µg/g in the presence of cystitis. These discrepancies seem to be attributable to the
difference in the severity of induced inflammation, in injection pressure as well as in the con-
centration of the drug in injected solution. It would seem that the same holds true with the
observed variations in the drug concentration in the serum. Anyhow, the blood levels of the
drug achieved under the conditions stated above are roughly estimated to be 150 µg/ml or so
in the rabbit, 50 µg/ml in the rat and 1.5~3.6 µg/ml in humans. One may thus be justified in
assuming that the permeability of the bladder to SBPC varies with different animal species,
being, for instance, high in rabbits and low in humans.

The intravesical injection of antibiotics as a means of treating clinical patients reportedly
was attempted by various authors, i.e., ADACHI6) (TC), KIRIYAMA4) (ABPC and KM) and
WADA15) and TÔMA16) (polymyxin B). ADACHI recognized the presence of TC in tissues of the
bladder resected after its intravesical injection, while KIRIYAMA demonstrated ABPC and KM in the serum following their intravesical injection. HARA reported that PLB was not found in the serum in any substantial amount after its intravesical injection. It should be mentioned, however, that HARA, WADA and TÔMA found this modality of treatment with the respective antibiotics to have proven effective against infection.

In our own cases of acute cystitis the effect of intravesically injected SBPC appeared to be fairly satisfactory for a single dose, but the antibiotic concentration in the serum was rather low and the urinary recovery of the drug was disproportionately low. From this it is inferable that much of the fraction transferred into bladder tissue was inactivated there. From combined consideration of these findings and those obtained in the aforementioned 11 cases it may safely be said that intravesically injected SBPC can permeate through the wall of the bladder with relative ease but its further spread into the circulation occurs to only a slight extent. Then, the intravesical injection of SBPC is considered to afford an advantage, over its administration by systemic routes, of proving effective in the treatment of infection, e.g. acute cystitis, in smaller doses and hence with a lower risk of producing adverse side-effects. The paucity of the drug appearing in circulation suggests that following the intravenous administration of SBPC the administered dose, for the most part, is eliminated in urine from the body and only a small fraction is absorbed from the wall of the bladder.

**Conclusion**

1. The absorption of SBPC from the bladder was studied in rats, rabbits and humans.
2. Rats received SBPC at intravesical doses of 12, 45, 24 and 300 mg. The amount of the drug transferred into the serum and its concentration in the wall of the bladder seemed to increase with increasing dose of the drug injected intravesically. However, the serum level of the drug tended to decline for 1–2 hours after dosing and rise thereafter, although the reason thereof is not known.
3. In rats with cystitis, the amounts of the drug transferred into the serum and bladder tissue were somewhat larger than, but not markedly different from, those in normal rats.
4. A similar experiment on rabbits demonstrated that both the serum and bladder tissue levels of the drug increased gradually for initial 4 hours following an intravesical dose. It became thus obvious that there is difference between these animal species in the pattern of absorption of the drug from the bladder.
5. Human subjects with acute cystitis were treated with a single intravesical dose of 1–5 g of SBPC. In more than half of the patients the treatment proved to be beneficial. This dose of the drug yielded rather low serum levels of the antibiotic and was associated with a urinary recovery rate of 45–65% in many instances.
6. In humans the intravesical administration of SBPC at a dose of 5 g yielded a concentration of the antibiotic in bladder tissue of around 8.6 µg/g.
7. SBPC, when injected intravesically, permeates through the wall of the bladder and eventually is transferred into the circulation. The fraction of a dose involved in these biological phenomena does not increase materially even in the presence of cystitis and seems to be determined largely by the dosage level of the drug.

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