Urol Res (1991) 19:297–300

Urological Research

Urease-induced precipitation of phosphate salts in vitro on indwelling catheters made of different materials

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Accepted: March 1, 1991

Summary. The urease-induced precipitation of phosphate salts on indwelling catheters was studied in an experimental in vitro model. The precipitation was strongly pH-related and was much higher in synthetic urine than in human urine. In the latter, it was significantly lower on silicone catheters than on latex catheters, including those with a hydrophilic coating. The precipitation on silicone catheters that had been in situ was not increased as compared with that on unused catheters, in contrast to latex catheters with a hydrophilic coating, among which the precipitation on used catheters was higher.

Key words: Indwelling catheters – Catheter encrustations – Urease

The use of indwelling catheters in the urinary tract for long periods is complicated by an encrustation of phosphate salts in certain patients; this applies to both urethral and ureteral catheters. The cause of the precipitation of these salts, which mainly include calcium phosphates and magnesium ammonium phosphate (MAP), is the infection with urease-producing microorganisms that is mostly associated with an indwelling catheter [4, 6, 13]. Urease splits urinary urea into ammonia, resulting in an alkaline pH and supersaturation and precipitation of the above-mentioned phosphates. The tendency to form catheter encrustations varies strongly among different individuals [7].

Experimental studies have shown that the precipitation of phosphates varies markedly among different urine specimens after inoculation of similar amounts of urease [9]. Urease-induced precipitation is more pronounced in urine containing high calcium and low protein levels and is minute in urine containing low calcium levels [9]. The large interindividual variation in the tendency to form catheter encrustations may consequently depend on differences in urine composition.

One way was to reduce catheter encrustations is to make catheters from a material that produces a surface with nonadherent properties. A limited number of clinical and experimental investigations have studied the variation of precipitation on catheters made of different materials [1, 2, 10]. However, there is evidence indicating that pure silicone catheters are associated with significantly lower adhesion than are latex and polyvinylchloride (PVC) catheters [1, 2]. Latex catheters coated with a hydrogel have recently been introduced. This coating absorbs liquid and makes the catheter soft and slippery, which can be assumed to make it less damaging to the urethral mucosa. Studies in synthetic urine, however, suggest that the coating does not render latex catheters more resistant to encrustations than are silicone catheters [3].

The present investigation was undertaken to compare the urease-induced precipitation of phosphate salts in both synthetic and human urine on catheters made of different materials and to study the dependence of such precipitation on urinary pH. We also studied the way in which precipitation on different types of catheters is influenced by their dwell time in patients.

Materials and methods

Human urine was collected as morning specimens from healthy individuals exhibiting negative urine cultures and no history of stone disease. The specimens were collected under sterile conditions, centrifuged at 3,500 rpm for 30 min at 4°C, filtered through a 0.22 µm millipore filter, pooled and immediately used. The synthetic urine used was prepared as described by Griffiths et al. [5], contained 11 solutes and displayed a pH of 5.8.

Catheters made of the following materials were studied:

1. PVC (Simplastic, J. G. Franklin and Sons)
2. Silicone (100% silicone catheters; Silicath, Travenol Laboratories Ltd.)
3. Latex with no coating (specially made for experimental use only; Bard Ltd.)
4. Latex with a hydrophilic polyurethane coating (Biocath, Bard Ltd.)
5. Latex, Teflon-coated (Bardco, Brd Ltd.)
6. Latex, silicone-coated (Norta, Beiersdorf AG)

Glass reactors were filled with 750 ml synthetic or human urine and placed in a water bath maintained at 37°C. Each reactor was sealed

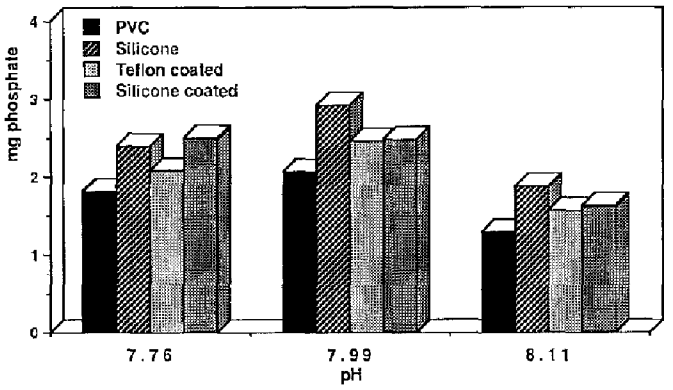

Fig. 1. The urease-induced precipitation of phosphate on catheters made of different materials at various pH levels

Table 1. The urease-induced precipitation of phosphate on unused catheters made of different materials following immersion in synthetic urine

Mean end pH ($n=10$)	Precipitation (mg/rod)		
	Latex with a hydrophilic coating	Uncoated latex	Silicone
7.9	1.4 ± 0.8	1.7 ± 0.9	1.7 ± 1
7.28	2.7 ± 0.5	3.8 ± 1.1	3.6 ± 0.9

with a glass cover, from which four solid glass rods extended down into the urine that filled the reactor. A 6-cm piece of the catheter (Charriere 16) to be studied was threaded onto each rod, and the catheter segment was thus completely covered with urine when the glass cover was placed on the urine-filled reactors. Jackbean urease (EC 3.5.1.5.; 1 unit = 1 mg $NH_3 \times 5$ min^{-1} at pH 7 and 30°C) was added, and after 4 h the pH was measured with a precision pH electrode (Orion 9-35, Orion Research Inc., USA). The encrustations on the catheter segments were dissolved in 15 M HNO_3 and analyzed for phosphate using a colorimetric method [14].

Experiment 1

The first set of experiments were performed to study the way in which the encrustation in synthetic urine differed on some of the more commonly used catheter materials and its dependence on the extent of the urease-induced pH increase. Two reactors containing synthetic urine were incubated simultaneously with the same concentration of urease. Each reactor contained a segment of catheter types 1, 2, 5 and 6. The urease concentrations used were 0.01, 0.015 and 0.02 units ml^{-1}. The results represented the mean of two experiments.

Experiment 2

This experiment was performed to investigate the effects on the catheters of prolonged immersion in infected urine. Catheter types 1, 2, 5 and 6 were immersed for 5 days at 37°C in human urine infected with Proteus mirbilis before being studied in the glass reactors. The catheters were then rinsed with sterile saline and one piece of each type was placed in the same reactor with urease-incubated (0.015 units ml^{-1}) synthetic urine.

Experiment 3

This series of experiments was undertaken to study the way in which the coating of a latex catheter with a hydrophilic material affected the precipitation in synthetic as well as human urine. In each reactor, one piece of the latex catheter (type 3), one piece of the 100% silicone (type 2) catheter and two pieces of the hydrophilic coated catheter (type 4) were placed. Ten experiments using synthetic urine and ten experiments using human urine were performed. The former studies used two concentrations of urease and the latter used only one.

Experiment 4

This experiment was performed to study whether the surface properties of silicone catheters and latex catheters with a hydrophilic coating were influenced by the catheters' having been in situ in the urethra. In each reactor we placed pieces of catheters (types 2 and 4) that had been in situ in patients for 2 weeks; as controls, pieces of unused catheters of the same types were used. Ten experiments using synthetic urine inoculated with urease at 0.015 units ml^{-1} were carried out.

Statistical methods

The precipitation of phosphate and the end pH were recorded as mean values ± SD. Differences were evaluted using Student's *t*-test.

Results

Experiments 1 and 2

Precipitation was most pronounced in synthetic urine incubated with 0.01 and 0.015 units urease, in which the end pH was 7.76 and 7.99, respectively. It was lower in urine inoculated with 0.02 units urease (end pH, 8.11; Fig. 1). The precipitation was the same on 100% silicone, Teflon and silicone-coated catheters. However, it was 20% lower on PVC catheters at all end pH values (Fig. 1). Immersion of the catheters in infected human urine did not change the precipitation on any type of catheter.

Experiment 3

Precipitation in synthetic urine was significantly lower ($P < 0.01$) on the unused hydrophilic coated catheters than on latex or 100% silicone catheters at both end values of pH (Table 1). The results of incubations with end values of pH between 7.16 and 7.4 are shown in Fig. 2. It can be seen that precipication was lower on the hydrophilic coated catheters in all but one of the ten experiments. However, no difference was noted between uncoated latex and 100% silicone catheters under the conditions of our test procedure. In human urine, the mean pH obtained

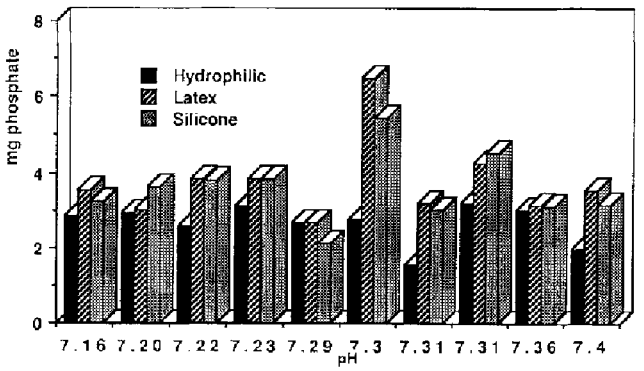

Fig. 2. The urease-induced precipitation of phosphate in synthetic urine on latex catheters with a hydrophilic coating as compared with that on an uncoated latex catheter and a silicone catheter: results of 10 experiments using the same amount of urease but resulting in various pH values

was 7.75 ± 0.37. Precipitation of phosphate was significantly lower ($P < 0.01$) on 100% silicone catheters (0.59 ± 0.29 mg) than on uncoated latex (0.73 ± 0.30 mg) or latex catheters with a hydrophilic coating (0.79 ± 0.39 mg). It is noteworthy that precipitation in human urine was less pronounced than that in synthetic urine.

Experiment 4

The mean end pH was 7.85 ± 0.17. The dwell time of a catheter in a patient did not influence urease-induced precipitation on 100% silicone catheters, which amounted to 2.38 ± 0.51 mg on used catheters and 2.53 ± 0.83 on unused catheters. Precipitation on catheters with a hydrophilic coating, however, was significantly higher ($P < 0.02$) on used catheters (2.46 ± 0.5 mg) than than on unused catheters (2.06 ± 0.58).

Discussion

As anticipated, precipitation of phosphates on the catheters was pH-related. It was less pronounced in human than in synthetic urine. In synthetic urine, it was significantly lower on PVC catheters and on unused hydrogel-coated latex catheters; however the difference between these and the other types of catheters, albeit statistically significant, was rather small. In human urine, precipitation was least pronounced on 100% silicone catheters. It did not increase on used catheters of this type. This contrasts with the hydrogel-coated catheters, on which precipitation not only was higher but showed an increase on used as compared with unused catheters.

The finding that precipitation in human urine was less pronounced on 100% silicone catheters than on the other catheters tested corroborates prior clinical studies [1]. That this property could not be reproduced in synthetic urine demonstrates that studies of this type should be performed in human urine, which better reflects the in vivo situation. This seems to be necessary despite the associated difficulties in standardization when results from different studies are to be compared.

Immersion of the catheters in infected urine did not produce an increase in precipitation. That the catheter had been in situ in a patient had no effect on 100% silicone catheters but tended to increase the precipitation on hydrogel-coated latex catheters. This suggests that the hydrophilic coating was lost or damaged during the catheter's dwell time in the urethra.

The amount of precipitation on an indwelling catheter depends on three factors:

1. The composition of the urine
2. The type of invading and colonizing bacteria, including their tendency to form biofilms and their potency as urease producers
3. The properties of the catheter used

The latter factor can be studied experimentally in synthetic or human urine inoculated with non-bacterial urease or with some of the urease-producing bacteria that colonize patients with long-term indwelling catheters.

The use of synthetic urine enables the experiment to be performed under standardized and reproducible conditions [3]. However, as synthetic urine does not contain the multitude of macromolecules that are present in human urine, it might not correctly reflect the situation in human urine. Our finding of lower precipitation on catheters with a hydrophilic coating as compared with other catheters in synthetic but not in human urine demonstrates this. Our results further support the view that investigators should be very careful in extrapolations based on findings obtained using synthetic urine. Human urine is preferable in spite of the methodological difficulties associated with its use.

When new catheter materials are introduced, they should be tested for their propensity to resist encrustation. According to the results of the present study, this should include testsof both unused catheters and catheters that have been in situ, and they should be performed in human urine.

The use of non-bacterial urease is another matter of discussion. It was used in the present study because it is available in pure, high-activity preparations. Its use made it possible to calculate the pH increase and obtain a reproducible estimate of urease-induced precipitation (Fig. 2). An attempt was made to prepare urease from *Proteus mirabilis*, but the amounts obtained were far too small to elevate the pH in human urine due to its high buffer capacity. However, the effect exerted by urease-producing microorganisms is not restricted to the breakdown of urea; their glycocalyx is also most probably involved in the formation of the catheter encrustations [12].

Hydrogel-coated latex catheters in synthetic urine were more resistant to encrustation, but this finding could not be reproduced in human urine. Other experimental studies have shown that there are no significant differences between the quantities of encrusting deposits occurring in silicone catheters vs hydrogel-coated latex catheters in artificial urine [3]. Furthermore, the precipitation increased if the catheters had been in situ. However, there

are other potential advantages for the use of this type of catheter, which, for example, exhibits a low degree of kinetic friction [11]. Nonetheless, many factors currently suggest that at least in cases involving long-term use, 100% silicone catheters remain an alternative, especially in patients in whom catheter encrustations constitute a problem.

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