Renal Damage Associated with Silicon Compounds in Dogs*

Paul M. Newberne and Robert B. Wilson

DEPARTMENT OF NUTRITION AND FOOD SCIENCE, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Communicated by Robert A. Alberty, January 19, 1970

Abstract. A number of oral preparations of various forms of silicon were fed to young adult Beagle dogs and young rats of both sexes for a period of four weeks. During the test period the animals were observed for clinical symptoms and urine and blood measurements were made. At the end of the experimental period all animals were sacrificed and subjected to a complete necropsy and histopathologic study. Polydipsia, polyuria, and soft stools in some animals fed sodium silicate and magnesium trisilicate were the only untoward clinical signs observed; all clinical tests on blood and urine were within normal limits. Gross and microscopic renal lesions were observed in dogs fed sodium silicate and magnesium trisilicate but no changes were seen in those animals fed silicon dioxide or aluminum silicate. Lesions were not observed in any of the rats. In view of the large number of commercial preparations which contain sodium silicate and magnesium trisilicate used in human medicine, these compounds deserve further study.

During the course of investigations into the effects of a number of metals on the kidney of the dog and rat, we observed subcapsular hemorrhage and tubular alterations along with moderate to severe reactive lesions of the renal interstitium in dogs fed relatively large doses of magnesium trisilicate and sodium silicate (unpublished data). Similar effects were not observed in rats. Since these two silicon compounds were the only ones in the group tested which were associated with renal lesions of any significance, experiments were repeated in which a number of oral preparations of various forms of silicon were fed to Beagle dogs and rats of both sexes. These included silicon dioxide, aluminum silicate, sodium silicate, and magnesium trisilicate. The results of these studies form the basis for this report.

Materials and Methods. Purebred Beagles of both sexes about 6 months of age and weighing 7–9 kg were purchased from a licensed breeder, vaccinated against leptospirosis, canine distemper, and hepatitis, and conditioned to 2 weeks in our laboratory. Since a preliminary experiment had shown that feeding or intubation resulted in an equivalent intake of compound and in equivalent renal lesions, for 4 weeks the dogs were fed a highly palatable diet1 in which the daily dose of the respective silicon compound was incorporated (Table 1). The doses administered provided in each case an approximately equivalent amount of silicon dioxide as the end product (0.8 gm/kg/day).

All animals were examined daily and weighed weekly. Urinary specific gravity and protein and glucose concentrations were measured before the tests began and at weekly intervals, along with total and differential white cell counts, packed cell volume, pro-
Table 1. Renal lesions in dogs fed silicon compounds for four weeks.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (gm/kg/day)</th>
<th>Sex</th>
<th>Incidence of renal lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>M</td>
<td>0/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>0/6</td>
</tr>
<tr>
<td>Silicon dioxide</td>
<td>0.8</td>
<td>M</td>
<td>0/9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>0/8</td>
</tr>
<tr>
<td>Aluminum silicate</td>
<td>1.3</td>
<td>M</td>
<td>0/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>0/7</td>
</tr>
<tr>
<td>Sodium silicate</td>
<td>2.4</td>
<td>M</td>
<td>8/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>7/8</td>
</tr>
<tr>
<td>Magnesium trisilicate</td>
<td>1.8</td>
<td>M</td>
<td>9/9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>9/9</td>
</tr>
</tbody>
</table>

Thrombin time, serum concentrations of hemoglobin and urea-nitrogen. At the end of the four weeks, the dogs were anesthetized with sodium pentobarbital, exsanguinated, and necropsied. Organ weights were determined, and a complete set of tissues preserved in formaldehyde solution for histopathologic examination.

Rats of both sexes of the Charles River Cesarean-Derived (CD) strain, weighing 80–100 gm, were fed the respective silicon compounds incorporated into a semisynthetic diet. Fifteen rats of each sex were fed each compound for 4 weeks in amounts equivalent to those fed to dogs. Clinical evaluations, necropsy procedures, and histopathologic examinations were the same as those for dogs.

Results and Discussion. The only significant clinical abnormalities exhibited by the dogs at any point during the four-week period were polydipsia and polyuria, observed in a few animals fed sodium silicate and magnesium trisilicate. Soft feces, discolored by unabsorbed compound, were seen occasionally in most treated dogs. Body weight, food intake, and urinary and blood measurements were essentially normal in all animals.

The only clinical symptoms observed in the rats were polydipsia, polyuria, and soft stools, seen intermittently in a few animals fed magnesium trisilicate or sodium silicate. All clinical chemical tests were within normal limits.

Gross cortical lesions of the kidney were observed in all male dogs, and in all but one female dog fed sodium silicate (Figs. 1 and 2). The lesions appeared to be focal, subcapsular hemorrhages but, on the cut surface, they suggested cortical infarcts. Similar lesions were seen in all animals of both sexes fed magnesium silicate or magnesium trisilicate. The lesions observed in dogs fed sodium silicate were characteristic of those seen in dogs fed sodium silicate or magnesium trisilicate. The appearance of the cut surface suggested cortical infarcts.
trisilicate but they were not observed in animals fed aluminum silicate or silicon dioxide.

Histopathologic studies revealed characteristic lesions in the kidneys of all dogs fed sodium silicate or magnesium trisilicate but none in any of the other groups. The nature of the lesion was the same in all cases, but severity varied from one animal to another and from one area to another within a kidney. Selected tubules were affected and were often in juxtaposition to normal ones (Fig. 3). Hypertrophy of tubular epithelium, with or without degenerative changes, inflammatory cell infiltration into the interstitium, and dilatation of some and collapse of other tubules were all observed to varying degrees within localized areas of the kidney (Fig. 4). Occasionally, deposits of crystalline material, characteristic of mineralization, were observed in degenerated tubular epithelium but such alterations were not common. Glomeruli did not appear to be damaged. The tubular lesions appeared to be reactive and were not considered to result from mechanical blockage, although an occasional tubule was apparently partially blocked by the hypertrophy and proliferation of regenerating epithelium. The general impression was one of irritation of tubular epithelium followed by degenerative and regenerative changes; these alterations were accompanied by inflammatory cell infiltration into the interstitium.
Despite the presence of extensive renal damage, impairment of renal function was not detected by any of the clinical tests conducted on serum or urine. Apparently, renal reserve was adequate for normal functional demands. Perhaps longer exposure to the compounds or examination of the animals after a longer period of time following termination of exposure would have revealed impairment of renal function associated with more advanced renal lesions.

There were no drug-related lesions in any of the rats. The only departure from normal observed in an occasional rat from each group was an isolated hyaline tubular cast.

We can only speculate on the mechanism of action of the two silicon compounds associated with renal lesions in the dog. Both of them were apparently absorbed from the gut and damaged the kidney as they or their metabolic products were excreted into the urine. Although the earlier reports of Mutch and Kraemer and Aaron stated that neither magnesium trisilicate nor the hydrated silica (SIO2) could be absorbed, the work of Page et al. showed conclusively that either magnesium trisilicate or one of its silica compounds is absorbed by human subjects and excreted in the urine as silica. Furthermore, Lagergren has reported urinary calculi, consisting mainly of silica, in five human patients, all of whom had been ingesting magnesium trisilicate tablets over several years. In contrast to the sparse information on urologic problems in man associated with silica, it is well known that calculi composed chiefly of silica are common in some animals and constitute a serious economic problem among cattle in many areas.

Although the rat was unaffected in these experiments, the unusual lesions in the kidney of the dog suggest a basic defect in the ability of this species to metabolize or excrete these compounds and present an interesting pathologic lesion for further study. The species difference observed in our studies in response to the silicates is interesting, and the rat data agree with similar negative observations in rats and mice reported earlier by Mutch. On the other hand, Settle and Sauer have shown that siliceous deposits form in the kidneys of guinea pigs given large doses of soluble silica orally or intraperitoneally. In view of the widespread use of various forms of silicon in products consumed by man, it would appear fruitful to investigate these compounds further in a broader spectrum of animal species.

* This work was supported in part by Department of Army Contract DA-49-193-MD2560.
5 Page, R. C., R. R. Hefner, and A. Frey, Am. J. Digest. Diseases, 8, 13 (1941).
12 Physicians Desk Reference to Pharmaceutical Specialties and Biologicals, 23rd edition, (Oradell, New Jersey) Medical Economics, Inc.