AN EXPERIMENTAL STUDY WITH PHENACETIN ON KIDNEY

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Phenacetin toxicity on kidneys was investigated in a study of white rats of both sexes, their weights ranging between 260–290 g.

Rats were divided into 2 groups according to drug dosage used: To group I, 10 mg/day and group II, 20 mg/day phenacetin was given. These dosages were 1/70 and 1/35 of animal lethal dosage, respectively and 2-4 times higher than the dosage therapeutically used in man. Since the weight differences were slight among animals in each group, same dosages were given to each animal in the same group. The drug was given in a pilule containing cheese and either 10 mg or 20 mg phenacetin. These pilules were eaten in the morning as the first meal. Dosage controls were done by urine examinations for N-Acetyl-P-Aminophenyl (APAP), a metabolite of phenacetin, using the Brodie and Avelrod method. APAP spectrophotometric values were measured after standard curves were prepared. Urine examinations were done 2 times daily and demonstrated the expected drug levels indicated by APAP control values.

Three animals in each group were investigated at the end of 2 months, 4 months and 6 months respectively. Using ethyl chloride narcosis after thoraco-abdominal incision, kidneys of animals were examined histopathologically.

Results

In group I (10 mg/day phenacetin) at the end of 2 months histopathological examination with light microscopy revealed oedematous glomeruli with capillaries full of red cells. Interstitium and tubules were normal. PAS and reticulum dyes gave normal histopathological findings.

In group II (20 mg/day phenacetin) at the end of 2 months histopathology revealed glomerular lobulation. Silver dye preparations exhibited an increase of reticular fibres of glomerular mesangium. Interstitium, blood vessels and tubules were normal in structure.

In group I, after 4 months, histopathological changes with light microscopy showed glomerular lobulation, red blood cell aggregations in the capillaries of glomeruli and accumulation of erythrocytes in the interstitium. Reticular
fibres were found to be increased when stained with reticulum dye. Proteinaceous material in medullary collecting ducts gave a PAS positive reaction.

In group II, at the end of 4 months light microscopic examination demonstrated glomerular findings similar to the ones seen after 10 mg/day treatment. Besides, lymphocytic infiltration in the interstitium and vacuolisation of tubular epithelium were noticed. Proteinaceous substance in collecting ducts was still evident but arcuate arteries were found to be normal.

In the first group at the end of 6 months histopathological examination revealed glomerular lobulation, more foci of interstitial lymphocyte infiltration and erythrocyte extravasation in the stroma. Lymphocytic infiltrations were also seen around vessels.

In group 2 at the end of 6 months histological examination showed glomerular lobulation and periglomerular round cell infiltrations and more interstitial lymphocyte infiltration compared with 4 months, and perivascular lymphocyte accumulation around a.arcuatae.

Discussion

This study demonstrated that phenacetin 2 and 4 times higher than the therapeutic dosage in humans, produced histopathological changes in rat kidney. Meyers and coworkers indicated that it was necessary to have about 1-44 years addiction period for the appearance of analgesic nephropathy. Schwangerber demonstrated that the nephropathy would develop if 1 g of phenacetin was given daily for one year. Our study exhibited histopathological changes even after 2 months. These findings suggest that it is not necessary to have a period of years for the development of the phenacetin nephropathy. Kincaid Smith reported that analgesics or their metabolites caused vasoconstriction in vasa recta and produced ischaemia of the papilla. Abrahams called this kind of papillary necrosis 'slow infarction'.

Although some investigators claim that the primary lesion begins in the medulla and then attacks the cortex, our findings indicated that the primary lesion began from the cortex. The appearance of the first lesion as glomerular lobulation and then the development of interstitial nephritis suggested the pathological events initiate from glomerular units. Perivascular infiltration of the a.arcuatae support the view of Abrahams that papillary ischaemia and slow infarction are the first steps.

References

Abrahams, C (1976) Lancet, ii, 346