

CURRENT SURVEY

Analgesic nephropathy and papillary necrosis

PRISCILLA KINCAID-SMITH

B.Sc., M.B., M.R.C.P., F.R.A.C.P., D.C.P.

*First Assistant in Medicine, University of Melbourne;
Physician-in-Charge, Medical Renal Unit, Royal Melbourne Hospital*

IT SEEMS likely from human and animal studies (Kincaid-Smith, 1967; Abrahams & Levin, 1967; Kincaid-Smith, Saker & McKenzie, 1968) that kidney damage resulting from a high analgesic intake in man and in animals can be explained on the basis of papillary necrosis followed by subsequent atrophy of adjacent cortical tissue. This concept makes it much easier to understand the possible mechanisms whereby analgesic-compounds may damage the kidney. Many substances are present in very high concentrations in the papilla, and it is reasonable to postulate that damage to the papilla may be related to high concentrations of some breakdown products of analgesic drugs.

This paper discusses possible mechanisms which may result in papillary necrosis in different conditions, with special reference to papillary necrosis associated with a high intake of various analgesic compounds.

Animal studies

Although many studies in animals have been inconclusive, a number of different workers have reported papillary necrosis following administration of analgesics (Clausen, 1962, 1964; Fordham Huffines & Welt, 1965; Fellers, Pradilla & Craig, 1965; Abrahams & Levin, 1967; Kincaid-Smith *et al.*, 1968). If one accepts that papillary necrosis is the primary lesion in analgesic nephropathy in humans, then it is true to say that comparable lesions to those seen in humans can be produced experimentally. The animal studies which have produced definite changes have been those in which the analgesic drug was given by gavage, and not mixed in the food. This may be relevant in that it is more likely to result in intermittent peak concentrations than is mixing the drug in the food. Intermittent dosage also gives a closer imitation of what happens in humans.

In a recent study in rats (Kincaid-Smith *et al.*, 1968) we have found lesions in the blood supply of the papilla which may well explain the mechanism where by analgesics damage the kidney.

After only 3 months on phenacetin and on a mixture of aspirin, phenacetin and caffeine in doses comparable with those taken by some of our patients, the rats showed definite lesions in the vasa recta. These lesions were more pronounced in rats which had been deprived of fluids overnight. The rats receiving aspirin, phenacetin and caffeine showed a different type of lesion from those receiving phenacetin alone. Four rats receiving aspirin, phenacetin and caffeine have developed papillary necrosis after only 6 months, whereas no animals receiving more than double the quantity of pure phenacetin have developed papillary necrosis. Cortical scarring could be clearly related to tubular atrophy in the nephrons interrupted by the necrosis in those animals which developed papillary necrosis.

Possible mechanisms of papillary necrosis

Necrosis of the renal papillae so closely resembles ischaemic infarction that it is difficult to accept that it can be a purely cytotoxic phenomenon.

It is very unlikely that a toxic effect would show a sharp line of demarcation between normal and dead tissue, such as is seen in papillary necrosis. This line of separation which is commonly at the junction of the outer third and inner two-thirds of the papillae does not correspond to the distribution of the spiral artery (Baker, 1959) and in acute papillary necrosis implies the sudden simultaneous cessation of blood flow in numerous vasa recta at a certain level in the medulla. The fact that the area supplied by the spiral artery, namely the tip of the papilla, is often preserved in analgesic nephropathy in man is evidence against the fact that lesions of this vessel contribute to papillary necrosis in humans.

In sickle-cell anaemia it is easy to understand the mechanism of sudden simultaneous occlusion of many vasa recta. The blood flow in the medulla is very slow, and any sudden lowering

of the oxygen tension, which is already low in the medulla (Leonhardt & Landes, 1963) may precipitate sickling in the vasa recta with resultant thrombosis and papillary necrosis. The oxygen tension would be the same in different vasa recta at the same level of the medulla, and it is thus quite easy to understand the sharp line which separates the necrotic papillae in sickle cell anaemia. It is reasonable to postulate that other forms of papillary necrosis may also result from interruption of blood flow in the vasa recta.

In urinary tract infection the vasa recta may be occluded by inflammation and swelling of the papilla, particularly as inflammatory lesions are commonly situated at the base of the papilla and in the outer medulla. Urinary tract infection may play a part in papillary necrosis in diabetes, although as papillary necrosis seems to occur in association with uncontrolled diabetes and marked hyperglycaemia, it is tempting to suggest that a very high concentration of sugar in the vasa recta may predispose to thrombosis in these vessels.

In analgesic nephropathy there is no clear-cut evidence of a relationship between excretion products of analgesic drugs and occlusion of vasa recta by thrombosis or some other process; however, our preliminary findings in animals suggest that this may be the mechanism which causes papillary necrosis (Kincaid-Smith *et al.*, 1968). Certain breakdown products of analgesics are known to cause haemolysis, and it is conceivable that a similar mechanism to that operating in sickle-cell disease could be responsible for thrombosis of vasa recta in analgesic nephropathy. Thromboses have, however, not been observed.

It is possible that when excretory products of analgesics reach a very high concentration in the papillae they precipitate out in the tubules, and possibly even in the interstitial tissue. This could invoke an inflammatory reaction which as either an acute or chronic phenomenon may compromise the blood flow in the vasa recta. A similar type of reaction could explain papillary necrosis associated with gout (Sanerkin, 1966). This mechanism was postulated on the basis of early lesions of analgesic nephropathy in human kidneys (Kincaid-Smith, 1967); however, our more recent findings in animals (Kincaid-Smith *et al.*, 1968) suggest that the vasa recta themselves may be the site of primary damage in analgesic nephropathy. The tubular and interstitial changes in the outer medulla which precede papillary necrosis could be secondary to ischaemia produced by impairment of the blood flow in the vasa recta.

It is possible to produce acute papillary

necrosis in animals in a number of different ways. Tetrahydroquinoline, vinylamine, phenothiazine-benzimidazol mixtures and human serum have all been shown to produce acute papillary necrosis in animals.

One of the most interesting and best-studied forms of experimental papillary necrosis is that produced by the intravenous injection of human serum into rats. Papillary necrosis develops and has been ascribed to occlusion of the medullary vessels (Wizgird, French & Coulson, 1965). Ljungquist & Richardson (1966) attributed serum-induced papillary necrosis to a cytotoxic effect; however, as stated above, it is difficult to accept a cytotoxic effect which produces a sharp line of demarcation between normal and necrotic tissue. Ljungquist & Richardson (1966) observed granular material in tubules and in vessels in the medulla, with considerable reduction in the vascularity of the papilla. It seems likely that this granular material, whatever its origin, interferes with the blood flow in the vasa recta.

Evidence which suggests that dehydration predisposes to papillary necrosis

Several unrelated facts suggest that analgesics and other substances are more likely to cause papillary necrosis in the presence of dehydration. This again suggests that the development of papillary necrosis is dependent in part upon the concentration of these substances within the papilla.

Experimental papillary necrosis induced in rats by the intravenous injection of human serum can be prevented by prior administration of mannitol, which would prevent high concentrations developing in the medulla (Ljungquist & Richardson, 1966).

A phenothiazine-benzimidazole drench which had been used previously without apparent ill-effect, caused widespread papillary necrosis in lambs in a very dry season in New Zealand (Prentice, personal communication 1967).

Renal papillary necrosis associated with analgesics seems to be far more common in Australia than in other countries. One possible explanation for this is that in all parts of Australia very high temperatures may occur in the summer months. Most people would become dehydrated from time to time under such circumstances, and this combined with a high analgesic intake could predispose to this type of renal damage. It seems likely that papillary necrosis is more common in Queensland than in Melbourne (Burry, 1966). Here again the warmer climate in Queensland could be a factor.

In patients with analgesic nephropathy, episodes of uraemia due to apparent fresh papillary necrosis may be precipitated by gastrointestinal haemorrhage. This again could reflect the effects of higher concentrations of some toxic substance in the medulla causing fresh damage.

Bluemle & Goldberg (1967) have shown that the very high concentrations of acetyl *p*-aminophenol, present in the medulla of the dehydrated analgesic-fed dog, are entirely abolished by hydration. Recent evidence in animals also shows that renal lesions are more severe in under-hydrated groups of rats receiving analgesics (Kincaid-Smith *et al.*, 1968).

All these unrelated facts suggest one measure which may protect against analgesic nephropathy. It is possible that even with a high intake of analgesics, one can avoid renal damage by maintaining a diuresis. This should allow the desired analgesic effect but diminish the nephrotoxic effects, and would be particularly useful in conditions such as arthritis, in which a high intake of analgesics may be essential.

What drug or drug combination causes papillary necrosis in analgesic nephropathy?

Although phenacetin has been widely blamed for the effects of analgesics on the kidney, the evidence against phenacetin does not warrant any firm conclusion at this stage. The main evidence against phenacetin is epidemiological, and rests on the fact that phenacetin is present in most analgesics which have been said to cause papillary necrosis. The main danger of accepting phenacetin as the cause of analgesic nephropathy lies in the implication that other analgesics are harmless. The evidence that other analgesics may cause serious renal damage is often overlooked (Kincaid-Smith, 1967). Salicylates alone may cause papillary necrosis both in man and in animals (Harvald, 1963; Fellers & Craig, 1963; Lawson & McLean, 1966; Olafsson, Gudmundsson & Brekkan, 1966); Prescott, 1966). There is, on the other hand, no evidence that phenacetin alone will produce papillary necrosis in man, as no preparation of pure phenacetin is available.

Our own recent findings (Kincaid-Smith *et al.*, 1968) confirm those of Abrahams & Levin (1967) that a high percentage of rats given aspirin, phenacetin and caffeine mixtures by gavage develop papillary necrosis. Abrahams & Levin (1967) found papillary necrosis in 62% of animals after 11 months, and we have found papillary necrosis in 44% of animals given aspirin, phenacetin and caffeine for 6 months.

We have not as yet observed papillary necrosis in animals receiving more than twice this dose of pure phenacetin. These findings suggest that some other ingredient in the aspirin, phenacetin, caffeine mixture either intensifies the effect of phenacetin or is itself nephrotoxic.

Phenacetin is immediately and quantitatively metabolized to paracetamol (Brodie & Axelrod, 1949) and the latter preparation should certainly remain under suspicion until the mechanism of analgesic nephropathy is clearly understood. Already one case of papillary necrosis has been attributed to paracetamol (Krikler, 1967) although the drug has been in use for a relatively short period of time.

It seems likely from clinical and experimental evidence that papillary necrosis may result from a variety of different substances. The common factor may be a non-specific irritant action produced by high concentrations of various substances acting perhaps on the endothelium of the vasa recta. We have recently heard of extensive papillary necrosis in the aboriginal woman addicted to soap! (G. Bauer, personal communication 1967).

Conclusions

The concept that analgesic damage to the kidney results from papillary necrosis, which in turn is probably due to interruption of the blood supply in the vasa recta, permits a simpler approach to the investigation of the possible mechanisms involved.

It seems likely that regardless of the exact mechanism whereby analgesics cause renal damage, a diuresis may offer some protection against this damage. Patients who require regular analgesics for the relief of pain should be advised to drink copious fluids, as this will not diminish the analgesic effect but reduce the concentration of breakdown products in the renal medulla.

Recent work in animals has shown lesions in vasa recta in animals receiving analgesic drugs which become apparent after as short a time as 3 months. These may well represent the primary lesion in analgesic nephropathy, particularly as a significant proportion of animals in the same experiment have subsequently developed papillary necrosis.

Acknowledgments

This work was supported by grants from the National Health and Medical Research Council of Australia, and the Wellcome Foundation.

References

- ABRAHAMS, C. & LEVIN, N.W. (1967) Personal communication.
- BAKER, S.B. DE C. (1959) The blood supply of the renal papilla. *Brit. J. Urol.* **31**, 53.
- BLUEMLE, L.W. & GOLDBERG, M. (1967) Mechanism of papillary necrosis in nephropathy of analgesic abuse. *Clin. Res.* **15**, 351.
- BRODIE, B.B. & AXELROD, J. (1949) Fate of acetophenacetin (phenacetin) in man and methods for estimation of acetophenacetin and its metabolites in biological material. *J. Pharmac. exp. Ther.* **97**, 58.
- BURRY, A.F. (1966) A profile of renal disease in Queensland. Results of an autopsy study. *Med. J. Aust.* **i**, 826.
- CLAUSEN, E. (1962) Nephrotoxic effect of phenacetin and acetylsalicylic acid in animal experiments. *Acta med. scand.* **172**, 419.
- CLAUSEN, E. (1964) Histological changes in rabbit kidneys induced by phenacetin and acetylsalicylic acid. *Lancet*, **ii**, 123.
- FELLERS, F.X. & CRAIG, J. (1963) Analgesic nephritis. *J. Amer. med. Ass.* **186**, 1610.
- FELLERS, F.X., PRADILLA, A. & CRAIG, J.M. (1965) The enhancement of salicylate toxicity by Diamox: chemical and morphological analysis. *Progress in Pyelonephritis* (Ed. by E. H. Kass), p. 337. Davis, Philadelphia.
- FORDHAM, C.C., HUFFINES, W.D. & WELT, L.G. (1965) Phenacetin-induced renal disease in rats. *Ann. intern. Med.* **62**, 738.
- HARVALD, B. (1963) Renal papillary necrosis. A clinical survey of sixty-six cases. *Amer. J. Med.* **35**, 481.
- KINCAID-SMITH, P. (1967) Pathogenesis of the renal lesion associated with the abuse of analgesics. *Lancet*, **i**, 859.
- KINCAID-SMITH, P., SAKER, B. & MCKENZIE, I.F.C. (1968) Lesions in the blood supply of the papilla in experimental analgesic nephropathy. *Med. J. Aust.* **i**, 203.
- KRIKLER, D.M. (1967) Paracetamol and the kidney. *Brit. med. J.* **i**, 615.
- LAWSON, A.A.H. & MCLEAN, N. (1966) Renal disease and drug therapy in rheumatoid arthritis. *Ann. rheum. Dis.* **25**, 441.
- LEONHARDT, K.O. & LANDES, R.R. (1963) Oxygen tension of the urine and renal structures. *New Engl. J. Med.* **296**, 105.
- LJUNGQUIST, A. & RICHARDSON, J. (1966) Studies on the pathogenesis of serum-induced renal papillary necrosis in the rat. *Lab. Invest.* **15**, 1395.
- OLAFSSON, O., GUDMUNDSSON, K.R. & BREKKAN, A. (1967) Migraine, gastritis and renal papillary necrosis. A syndrome in chronic non-obstructive pyelonephritis. (Personal communication).
- PRESCOTT, L.F. (1966) Analgesic abuse and renal disease in North Scotland. *Lancet*, **ii**, 1143.
- SANERKIN, N.G. (1966) Chronic phenacetin nephropathy. *Brit. J. Urol.* **35**, 361.
- WIZGIRD, J.P., FRENCH, S.W. & COULSON, W. (1965) Pathogenesis of serum-induced papillary necrosis. *Arch. Path. (Chic.)*, **79**, 57.