Papers and Originals

Phenacetin Nephropathy, with Particular Reference to the Effect of Surgery

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British Medical Journal, 1970, 4, 131-134

Summary: Sixteen patients suffering from phenacetin nephropathy were seen at one London hospital between June 1964 and January 1970. There were five deaths, three of them following a surgical operation. Phenacetin nephropathy occurs far more frequently than is generally considered. Unless patients are asked about the consumption of phenacetin routinely the diagnosis is usually missed. It is recommended that phenacetin and paracetamol should be available only on a doctor's prescription.

Introduction

Phenacetin nephropathy was first described by Spühler and Zollinger (1953). The number of patients suffering from phenacetin nephropathy who have been reported is several thousand (Shelley, 1967). Most of these have occurred in Australia (Burry, 1967; Pearson, 1967). Switzerland (Dubach *et al.*, 1965; Gsell *et al.*, 1968), and the Scandinavian countries (Nordenfelt and Ringertz, 1961; Kasanen *et al.*, 1962; Grimlund, 1963). Relatively fewer cases have been reported from North America (Harrow, 1967; Gault *et al.*, 1968; Koch *et al.*, 1968). In Great Britain, however, only 117 cases of phenacetin nephropathy have been reported, of which 89 have come from Scotland (Brown and Pell-Ilderton, 1964; Jacobs, 1964; Sanerkin and Weaver, 1964; Beales, 1965; Kennedy, 1965; Lawson and MacLean, 1966; Prescott, 1966; Sanerkin, 1966; Cochran *et al.*, 1967; Dyer and Lee, 1967; Hulme and Jones, 1967; McMillan *et al.*, 1968; Bell *et al.*, 1969a). More recently the conclusion that phenacetin causes renal disease has been obscured by the implication that it is harmful only if ingested with some other substance.

The incidence of phenacetin nephropathy is unlikely to be as negligible in Great Britain as the figures mentioned above would suggest, for the consumption of phenacetin per head of population in Great Britain is substantial. In the past few years we have become increasingly aware that the incidence of the disease is far greater than has been thought. We have been particularly impressed by the deleterious effects of surgery on these patients.

Patients and Clinical Details

Between June 1964 and January 1970 phenacetin nephropathy was diagnosed in 16 patients attending Fulham Hospital, of whom four were men and 12 women aged 36 to 63. None was suffering from diabetes or tuberculosis. They presented with loin pain, haematuria, urinary infection, and symptoms of advanced renal failure and hypertension. All but three patients had had nocturia for several years before coming to hospital, but none had thought it worth mentioning to their doctors; nine patients had had bouts of severe dyspepsia;

two patients drank a great deal of alcohol, three others were severely depressed; and one had had an episode of acute delusional psychosis.

All the patients took analgesic tablets which contained 250 mg. of aspirin and 250 mg. of phenacetin per tablet. The estimated ingestion of phenacetin in 14 of the 16 patients varied from 2 to 25 kg. taken over 3 to 20 years. In one of the other two patients the diagnosis of phenacetin nephropathy was made only at necropsy. A retrospective history from the relatives and medical records indicated that he had consumed large amounts of phenacetin for osteoarthritis for at least five years; but it was not possible to obtain a more precise estimate of the amount ingested. One patient had consumed 1 kg. of phenacetin in three years while temporarily working on the shores of the Red Sea at Aden; she also admitted that at all times she drank only small amounts of fluid.

The stated reason for starting to take analgesic tablets in such patients was joint pains (rheumatoid arthritis in three, ankylosing spondylitis in three, and osteoarthritis in one) and backache in two; six had started because of headaches; the other patient had had persistent pain from an ununited fracture. In three of the patients the ingestion of phenacetin had ceased 5 to 10 years before phenacetin nephropathy had been diagnosed, though renal failure had been detected in the interval. Four of the nine patients with dyspepsia died. At necropsy there was no scarring or ulceration of the stomach or duodenum. Barium meal examination in the other five patients was normal.

In those patients who stated that they had stopped taking phenacetin, and who were followed up for more than one year, renal function appeared to remain unchanged or to improve.

Renal Function and Intravenous Pyelogram

With two exceptions, all patients had a plasma creatinine greater than 1.5 mg./100 ml. The mean plasma creatinine was 5.0 mg./100 ml. with a range of 9.2 to 0.8 mg./100 ml. The ability to concentrate was severely impaired in all the seven patients in whom this test was performed. Two of these seven had plasma creatinines of 1.8 and 0.8 mg./100 ml.; they were unable to concentrate above 400 m-osmole/kg. H₂O. The ability to acidify the urine was severely impaired in four of the five patients in whom the test was performed.

Persistent proteinuria was present in 8 of the 16 patients. At times when the urine was uninfected 11 of the 16 had a persistently high white cell excretion rate (greater than 400,000/hour or more than 10/mm.³). On occasion, 7 of the 16 patients had a urinary infection (midstream specimen of urine with over 100,000 organisms/ml.), but when the infection was controlled the white cell excretion rate fell to normal in only three.

The intravenous pyelogram in 9 of the 11 patients who are still alive showed loss of one or more papillae with caliceal clubbing. In the other two patients the kidneys were

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less than 8.5 cm. long and the caliceal patterns were not discernible. The kidneys of all five patients who died showed widespread destruction of the papillae, which were either necrotic or absent.

Effect of Surgery

Seven patients underwent some surgical procedure under a general anaesthetic. In three of them the operation was followed by a severe deterioration of renal function. A short account of these three patients is given below.

Case 1.—A 62-year-old known alcoholic who had ingested large amounts of phenacetin for over five years developed acute renal failure following a repair of the left rotator cuff. He was treated with haemodialysis for three months. For the next three years the plasma creatinine remained at 7.0 mg./100 ml. Barium meal examination was normal. He died of an acute respiratory infection, and at necropsy most of the papillae were black and leathery; the others were absent.

Case 2.—A 47-year-old housewife had ingested 5 kg. of phenacetin in five years and had also consumed much whisky. She had a plasma creatinine of 4.2 mg./100 ml. with gross impairment of the ability to concentrate, and sterile pyuria. She was anaemic and hypertensive. Barium meal examination was normal. Her renal function suddenly deteriorated after a surgical operation, during which she suffered from a 10-minute period of anoxia due to delayed recovery of spontaneous respiration. She recovered gradually but died of cardiac arrest. At necropsy the papillae were either absent or shrunken and calcified.

Case 3.—A man of 63, who had ingested 5 kg. of phenacetin in four years for rheumatoid arthritis, was admitted to hospital because of vomiting and loss of weight. Barium meal examination showed an ulcer crater at the pylorus. Blood urea was 176 mg./100 ml. Laparotomy revealed no abnormality and pyloroplasty was performed. Postoperatively the blood urea rose to 320 mg./100 ml. and the creatinine clearance fell to 2 ml./min. He died a few days later. Necropsy showed small kidneys with necrotic or absent papillae; the stomach was normal.

Patients with Suspected Analgesic Nephropathy

Over the same period we have seen several other patients not included above, from whom it has either been impossible to obtain a sufficiently precise history of a high consumption of analgesics or, since the patient was first seen in advanced renal failure, it was impossible to make a satisfactory radiological examination of the kidneys. Nevertheless, the available data obtained from such patients have supported the possibility that they were suffering from phenacetin nephropathy.

Discussion

There is a myth that in Great Britain phenacetin nephropathy is rare and occurs mainly in Scotland. This presumably stems from the fact that only 28 cases have been reported from England and Wales since 1964 (Brown and Pell-Ilderton, 1964; Jacobs, 1964; Sanerkin and Weaver, 1964; Beales, 1965; Kennedy, 1965; Sanerkin, 1966; Dyer and Lee, 1967; Hulme and Jones, 1967; Bell *et al.*, 1969b). Only one case has been reported from London (Dyer and Lee, 1967). In addition, the Registrar General's *Statistical Review for England and Wales* lists only five deaths due to the adverse effect of phenacetin in 1966 (General Register Office, 1970).

It is clear that the true incidence of phenacetin nephropathy is much greater than the reported incidence would suggest. The 16 patients described here were all seen at one small hospital in the London area between June 1964 and January 1970. Admittedly we are likely to see more of these patients because of our interest in renal disease. Nevertheless, 7 of the 16 patients were first seen by other departments before they

were referred to us—that is, about one per year. None was referred from the paediatric or geriatric wards. They therefore came from the other 191 beds in the hospital which are in medical, surgical, urological, or orthopaedic wards. The total number of such beds listed in the *Hospitals Year Book 1966* (p. 396) in England and Wales was 89,083. If we assume an incidence of one new patient for 200 such beds per year throughout the country the overall incidence of new patients in England and Wales suffering from phenacetin nephropathy would be around a minimum of 450. This incidence excludes those cases which are likely to be referred to departments of nephrology, of which we had nine during the same period. If these assumptions are only partially accepted it would seem that the total incidence of new patients presenting with phenacetin nephropathy in England and Wales is unlikely to be much less than 500 per year. In this connexion it is interesting that between 1964 and 1967, during which five of our patients died of phenacetin nephropathy, only three died of chronic pyelonephritis.

One of the main reasons why the incidence of phenacetin nephropathy appears so low is that unless the diagnosis is suspected it is missed. The following case illustrates how easy it is to do this:

Case 4.—A 35-year-old woman with advanced renal failure died of a staphylococcal pneumonia in November 1969. In October 1961 she had sustained a fracture of the right radius which needed the insertion of a metal plate. Two years later she developed hypertension, marked nocturia, and a blood urea of 50 mg./100 ml. Though the urine was sterile she had pyuria and was therefore treated with antibiotics. Renal function deteriorated steadily thereafter. At necropsy the papillae of both kidneys were either absent, or necrotic, or calcified. Her husband was told that the necropsy confirmed that death was due to septicæmia and that the kidneys were small. But he was not told that the appearances suggested that his wife might have ingested large quantities of phenacetin. In the subsequent conversation, however, he spontaneously stated that when his wife had first developed renal failure he had read a book on renal disease. This had led him to the tentative conclusion that she was suffering from phenacetin nephropathy. He said that in 1961 she had started to take large quantities of phenacetin-containing products because of the pain of the orthopaedic plate in the right radius. She had then taken increasing amounts for headaches and finally for both headache and backache. From his account it was calculated that she had consumed between 3.5 to 5 kg. of phenacetin in eight years. He had not mentioned these facts to anybody previously for he did not think that his clinical deductions could be of any medical value.

Despite the frequent complaints of indigestion it is remarkable that there was no evidence of peptic ulceration in any of the five patients who were examined at necropsy or in the eight others who had had a barium meal examination. This is in line with the other cases reported from England and Wales, but is in striking contrast to the frequent association between peptic ulceration and phenacetin nephropathy in Australia and Canada (Dawborn *et al.*, 1966; Gault *et al.*, 1968).

Of the seven patients described here who had had a surgical operation three developed a sudden deterioration of renal function after operation and died subsequently. The deleterious effects of surgery in patients who consume large quantities of phenacetin can also be discerned in the account of Dawborn *et al.* (1966). Over a four-year period they treated 30 patients who were persistent phenacetin ingesters and who also suffered from a peptic ulcer. Eighteen of these had had a gastrectomy, 10 of them dying some time after operation. These facts suggest that surgical operations and their aftermath may cause a sudden widespread necrosis of existing papillae. Such a hypothesis is in keeping with what is known of the development of phenacetin nephropathy and of the effect of surgical operations on the renal and medullary circulation of normal kidneys.

Much evidence suggests that the gradual destruction of the papillae caused by persistent phenacetin ingestion is due to

an ischaemic process. The earliest lesions in both man and the rat are situated in the centre of the papillae—that is, in the area most distant from the main vessels (Lindvall, 1960). Initially the tip of the papilla, which has its own direct blood supply, is not involved (Baker, 1959). Kincaid-Smith *et al.* (1968) showed that in the rat the first structural abnormality is a diminished number of patent vessels in the bundles of the vasa recta together with a reduction in size of the individual vessels. Similarly, Lagergren and Ljungqvist (1962) found that in nine patients who had ingested large quantities of phenacetin the vasa recta in the centre of the papillae were generally hyalinized and bloodless, whereas in the periphery they were tortuous and congested. In addition, the central distribution of the necrosis in the papillae of phenacetin nephropathy is the same as that which occurs in the papillary necrosis of sickle-cell anaemia, in which the sickle cells occlude the vasa recta (Harrow, 1967).

The deleterious effects of surgery on the kidney are due to dehydration and renal ischaemia. In man dehydration increases the incidence of phenacetin nephropathy (Burry *et al.*, 1966; Kincaid-Smith, 1969); and all experimental work in which phenacetin alone has been given confirms that papillary lesions are more pronounced in dehydrated animals (Kincaid-Smith *et al.*, 1968). This is consistent with the demonstration that the metabolic end-product of phenacetin is concentrated selectively in the renal medulla during dehydration (Bluemle and Goldberg, 1968). During surgical operation overall renal ischaemia is due to the anaesthetic agents (de Wardener, 1955) a high PCO_2 (Stone *et al.*, 1958), and blood loss (Lauson *et al.*, 1944). In addition, surgical operations and the postoperative period are characterized by a high concentration of circulating antidiuretic hormone (Chalmers and Lewis, 1951; Deutsch *et al.*, 1966; Bartter and Schwartz, 1967), which causes medullary ischaemia (Thurau, 1964; Fourman and Kennedy, 1966). Thus in a patient with pre-existing ischaemic lesions of the renal medulla caused by excess ingestion of phenacetin the superimposed dehydration and renal ischaemia associated with a surgical operation may precipitate papillary necrosis.

Phenacetin and Other Analgesics

The evidence that phenacetin is the cause of analgesic nephropathy is increasingly compelling. Analgesic tablets can be divided into those that contain several ingredients, such as caffeine, phenacetin, aspirin, phenazone, aminopyrene, and codeine, and those that contain only one ingredient. The bulk of phenacetin is ingested in preparations which contain several ingredients, whereas aspirin, for instance, is sold mainly in a single preparation. Nearly all patients suffering from analgesic nephropathy have therefore ingested tablets which contain phenacetin and one or more additional ingredients. In some countries, including Great Britain, the most common mixture has been phenacetin and aspirin, with or without caffeine or codeine. In Switzerland it has been phenacetin and caffeine (Dubach *et al.*, 1965) and in Sweden phenacetin, caffeine, and phenazone (Grimlund, 1963).

With very rare exceptions none of the additional ingredients when taken in mixtures or alone cause papillary necrosis in man in the absence of phenacetin (Scott, 1966). The most interesting substance in this respect is aspirin, for its consumption in Great Britain is about six times that of phenacetin—for example, in 1967 the consumption of phenacetin was about 540,000 kg. and that of aspirin, 3,020,000 kg. Nevertheless, though the annual consumption of aspirin by itself is more than 2,000,000 kg. per year, there have been only two cases reported of papillary necrosis due to aspirin ingestion (Lawson and MacLean, 1966; Prescott, 1969). One other patient in whom this diagnosis was first made (Lawson and MacLean, 1966) was subsequently found to have methaemoglobinaemia (A. H. H. Lawson, personal communication to J. T. Scott), a well-known complication of

excess phenacetin ingestion. Only three other cases have been reported in world medical literature (Olafsson *et al.*, 1966; Harvald, 1963). Ross (1962) pointed out that in Australia the consumption of aspirin by itself was very great, and yet from that continent there have been no reported cases of papillary necrosis due to prolonged aspirin ingestion.

Epidemiologically, therefore, it appears that analgesic papillary necrosis is due to the ingestion of phenacetin. As phenacetin, however, is nearly always taken with other substances it is not clear whether its destructive effect is due to phenacetin by itself or whether it is destructive only in the presence of some other substance. The ingestion of phenacetin alone is so uncommon that it has not been possible to determine whether it may cause papillary necrosis by itself in man. On the other hand, the hypothesis that phenacetin can destroy only in the presence of some other substance has to explain why such different substances as caffeine, phenazone, aspirin, aminopyrene, and codeine all appear to be effective. These doubts should not obscure the overriding fact that it is the presence of phenacetin with which the destruction of the renal papillae in man is associated.

The average ingestion of phenacetin in Great Britain was about 12 g. per head of population in 1964 and about 8 g. in 1967, and since then it has remained at about this level. As there is about 250 mg. of phenacetin in each phenacetin-containing tablet this represents an average intake per year for each man, woman, and child in Great Britain of 48 tablets containing phenacetin in 1964 and 32 tablets in 1967 and each year thereafter. These phenacetin-containing tablets were available either as proprietary products or as *B.P.* or *B.P.C.* preparations. To find out the proportion of phenacetin in each product ingested in 1964 and 1967, letters were written to the 70 firms which at that time were manufacturing the 110 proprietary analgesic preparations containing phenacetin. They were asked how many tablets or other phenacetin-containing preparations they had sold during 1964 and 1967. Only 21 firms answered the questions. These included all but one of the major suppliers, about which, however, information was obtained from another source. The dominant downward trend in the consumption of phenacetin which was mentioned by the bulk suppliers was borne out in the information obtained from those manufacturers who answered.

Unfortunately it was not possible to obtain precise information on the amount of phenacetin imported as finished products. For instance, one of the major suppliers regretted that they were "unable to supply any valid information of the type required." Nevertheless, the important and clear-cut conclusion which emerges from the answers obtained, and all other sources of information, is that more than four-fifths of the phenacetin ingested in Great Britain in 1964 and 1967 was obtained in the form of *B.P.* or *B.P.C.* preparations and only one-fifth as proprietary preparations.

Animal Studies

It is difficult to assess the relevance of animal experiments to the incidence of papillary necrosis from phenacetin-containing mixtures in man. Rats (Singh *et al.*, 1969) and rabbits (Chausen, 1964), in contrast to man, develop papillary necrosis when given acetylsalicylic acid. Therefore the finding that combinations of phenacetin and acetylsalicylic acid regularly produce necrosis of the papillae in rats (Abrahams *et al.*, 1963; Kincaid-Smith *et al.*, 1968; Singh *et al.*, 1969) is not relevant to what happens to man in the same circumstances.

In other animal studies phenacetin alone has been given. Again it is difficult to assess what relevance these have to the disease in man, for this is not the way phenacetin is ingested by man and there may be species differences in response. Nevertheless, the results are interesting and suggestive. With phenacetin alone Abrahams *et al.* (1963), Fordham *et al.* (1965), and Kincaid-Smith *et al.* (1968) produced some lesions in the renal medulla, these being more pronounced in

dehydrated animals. Papillary necrosis, however, has only rarely been induced by phenacetin alone (Fordham *et al.*, 1965). In a most interesting observation in dogs Bluemle and Goldberg (1968) gave a single dose of either phenacetin or aspirin and removed a kidney two hours later. They then estimated the concentration of *N*-acetyl-*p*-aminophenol and salicylates in various parts of the kidney. *N*-acetyl-*p*-aminophenol is the end-product of most of the phenacetin that is absorbed, the conversion taking place within two to four hours after absorption. In dehydrated animals *N*-acetyl-*p*-aminophenol was concentrated in the papilla 10 times more than in the cortex, possibly because it is a chemical analogue of urea. In hydrated animals, however, the concentration of *N*-acetyl-*p*-aminophenol in the medulla and the cortex was the same as that in plasma. Aspirin was not concentrated in the medulla in either hydrated or dehydrated animals.

N-acetyl-*p*-aminophenol is the substance which is also known as paracetamol and is marketed under many trade names. There appears to be no logical reason to believe that its effect on the kidneys is any different from that of phenacetin. Paracetamol, however, has not been in use long enough to settle this point conclusively. On the other hand, one case of papillary necrosis following the prolonged ingestion of paracetamol has already been reported in Great Britain (Krikler, 1967); and two others are about to be reported (Kerr, personal communication). In addition, Kincaid-Smith (1969) observed that patients suffering from phenacetin nephropathy failed to improve in the usual way when they stopped taking tablets containing phenacetin, if they replaced these with paracetamol.

The consumption of both phenacetin and paracetamol must be reduced by all means available. So far as it has been possible to assess, at least 10 firms—including most of the big suppliers—have ceased to use phenacetin in their proprietary preparations in the past few years. This excellent decision is to be encouraged, but it can do little to affect the total ingestion of phenacetin for, as pointed out above, more than four-fifths of the phenacetin ingested in Great Britain is taken in B.P. and B.P.C. preparations. Obviously to reduce the consumption of phenacetin substantially it will have to be removed from the B.P. and B.P.C. preparations in common use. In this group of hospitals, for instance, phenacetin was removed from tab. codeine co. and tab. A.P.C. two years ago.

The evidence against phenacetin is such that if it had been suspected of causing papillary cancer, as opposed to papillary necrosis, it would have been prohibited some years ago. Cyclamates, which had not been suspected of causing harm to man, were recently banned on what many considered to be inadequate evidence of its harmful effects in animals (*British Medical Journal*, 1969). Presumably phenacetin has not been banned, for it seems to be harmful only to man, whereas animals are relatively immune. These decisions seem to be influenced by a belief that it is more natural and acceptable to die of renal failure than of cancer. Bell *et al.* (1969b), discussing phenacetin nephropathy, stated that "the practising physician cannot wait for final proof; he must make an interim judgement and advise his patients." Surely the onus of proof is now squarely on those who would allow the continued and indiscriminate use of phenacetin and paracetamol to prove that they are not harmful to man. In the meantime phenacetin and paracetamol should be available only on a doctor's prescription.

ADDENDUM: Since this paper was drafted we have seen three additional patients suffering from phenacetin nephropathy, and there has been one more death among the patients reported. The death occurred two weeks after a surgical operation. Out of a total of six deaths, therefore, four occurred soon after a surgical operation.

We wish to thank Dr. A. L. Wyman, Mr. C. G. Hopper, Mr. B. Armitage, Miss M. Garland, Miss M. Nichols, and Mrs. E. Hobbs for their help and co-operation. We are also grateful to many members of the pharmaceutical industry for their assistance in obtaining valuable information.

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