Effects of analgesics and related compounds on renal metabolism in rats

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Summary

1. The metabolic effects of p-aminophenol have been compared with those of paracetamol and other analgesics in studies of rat liver and kidney in vitro.

2. p-Aminophenol injected into rats inhibited gluconeogenesis from lactate in renal cortical tubules, but not in isolated hepatocytes, and reduced kidney ATP content without affecting the ATP content of liver. Perfused kidneys from rats previously injected with p-aminophenol showed a 50% reduction of ATP content, severe inhibition of Na+ reabsorption and reduction of inulin clearance without significant inhibition of gluconeogenesis from lactate.

3. Paracetamol, p-phenetidine, phenazone and aspirin, when given intravenously to rats, had no effect on renal tubular glucose synthesis from lactate or pyruvate. Paracetamol and aspirin both slightly inhibited renal glucose synthesis from several different substrates when added directly to tubules.

4. Paracetamol (4 mmol/l) inhibited glucose synthesis from lactate and other substrates by 50% or more in isolated hepatocytes. Glucose synthesis from lactate was inhibited 30% by concentrations of paracetamol as low as 0.5 mmol/l.

5. These results indicate that p-aminophenol is a potent inhibitor of proximal tubular function, with its main site of action the inhibition of ATP synthesis and energy production, and they confirm the primary hepatotoxic effect of paracetamol.

Key words: p-aminophenol, analgesic nephropathy, gluconeogenesis, renal metabolism.

Introduction

Many patients abusing compound analgesics develop chronic renal disease. Its cause and course are poorly understood. Because patients are often seen with established renal failure, and analgesics have been taken for many years, it is assumed that the natural history of the disease is gradual and progressive. This may not be correct. The cortical component of the kidney lesion, interstitial nephritis, may follow acute tubular necrosis (Hollman & Wong, 1964; Green, Ham & Tange, 1969). Little is known of the way in which analgesics produce renal damage. Individual analgesics are either not nephrotoxic, even in very high doses (Leonards, 1972; Phillips, Hartnagel, Leeling & Gurtoo, 1976), or produce minor renal damage (Fordham, Huffines & Welt, 1965; Nanra & Kincaid-Smith, 1970) insufficient to cause renal failure. Moreover, paracetamol, the major metabolite of phenacetin, is hepatotoxic (Dixon, Nimmo & Prescott, 1971) and not nephrotoxic. The hepatotoxicity of paracetamol has been investigated in detail (Gillette, 1974; Jollow, Thorgeirsson, Potter, Hashimoto & Mitchell, 1974), and may be due to the formation of a toxic intermediate metabolite, which is very reactive chemically, and which accumulates in toxic concentrations only when primary meta-
bolic pathways are already saturated. Formation of similar highly reactive intermediate metabolites of phenacetin can be deduced from the presence of certain minor metabolites in the urine (Nery, 1971; Calder, Creek & Williams, 1974), and some related compounds which are highly nephrotoxic (Calder, Funder, Green, Ham & Tange, 1971) may be responsible for the supposed nephrotoxic effect of phenacetin.

*p*-Aminophenol is chemically related to phenacetin and is a potent nephrotoxin. Even in small doses it produces necrosis of proximal convoluted tubules in rats, but animals survive quite large doses (Green et al., 1969). Ultrastructural studies show changes in affected cells within 30 min of intravenous injection (Funder, Green, Ham & Tange, 1972), and complete necrosis develops in some cells within 4 h. We aimed to determine if biochemical and functional changes accompany or precede the appearance of these lesions, by studying biosynthetic function and ATP in vitro in isolated rat liver cells and renal cortical tubules, and also measuring transport and metabolism in the isolated perfused kidney.

**Methods**

**Animals**

Male albino Wistar rats, weighing 250–350 g, were fed on a pellet diet (Labsure 41B) and starved for 24 h before experiments, being allowed access to water. Animals (six to eight in each group) were given (dose 3 mmol/kg) *p*-aminophenol, *N*-acetyl-*p*-aminophenol (paracetamol), phenazone or *p*-phenetidine [all as the hydrochloride, 1 mmol in 1 ml of HCl (1 mol/l)] or acetylsalicylic acid [aspirin, as sodium salt: 1 mmol in 1 ml of NaOH (1 mol/l)], by tail vein under light ether anaesthesia. The volume of each injection was approximately 1 ml, given at 0.2 ml/min. Under these conditions, *p*-phenetidine was often fatal. Control injections of HCl or NaOH had no deleterious effects on the animals. Liver cells and renal tubules prepared from such animals gave the same rates of gluconeogenesis as those from control rats.

Both injected and normal animals were given intraperitoneal pentobarbitone (60 mg/kg) for preparation of isolated renal tubules or liver cells, or liver and kidney tissue for ATP determinations, or for isolated kidney perfusion.

**Isolated tissues**

Isolated renal tubules were prepared by a modification (Dr P. Vinay, personal communication) of previous methods (Guder, Wiesner, Stukowski & Wieland, 1971). Slices of renal cortex were incubated for 45 min in a 150 ml siliconized conical flask containing 30 mg of hyaluronidase (EC 3.2.1.35) and 10 mg of collagenase (EC 3.4.24.3) (Boehringer, Mannheim) in 10 ml of Krebs–Henseleit medium. The final suspension contained 15–30 mg dry weight of tubules/ml. Portions of suspension (0.5 ml) were added to 25 ml siliconized conical flasks containing 0.5 ml of 10% dialysed serum bovine albumin, 0.1 ml of substrate (0.2 mol/l lactate, pyruvate etc.) and 0.9 ml of Krebs–Henseleit medium. The flasks were gassed with O₂/CO₂ (95:5, v/v) for 45 s, stoppered and then incubated at 37°C for 40 min in a shaking water bath at 90–100 oscillations/min. Reactions were stopped by adding the contents of the flask to 0.5 ml of perchloric acid (1 mol/l). Dry weight of renal tubules was determined by evaporating duplicate 1 ml portions to dryness. No correction was made for the mineral weight of the suspending volume of medium; this results in a 5–10% over-estimate of the tissue dry weight. Test compounds were added in 2 or 4 mmol/l concentrations.

Liver cells were prepared by the method of Berry & Friend (1969), as modified by Krebs, Cornell, Lund & Hems (1973), portions of the suspension being incubated with substrate as for the isolated renal tubules. Test compounds in aqueous solution were added to preparations of liver cells from normal uninjected animals. Results were expressed as μmol of product/g dry weight.

Isolated kidneys were perfused by the method of Nishitstsutsui-Uwo, Ross & Krebs (1967), as modified by Ross, Epstein & Leaf (1973), via the renal artery with a medium consisting of 6.7% bovine serum albumin (fraction V) in Krebs–Henseleit medium. Substrate, either lactate (10 mmol/l) or glucose (5 mmol/l), was added before beginning perfusion, and perfusion was continued for 60 min. Glomerular filtration rate (inulin clearance) was determined with [¹⁴C]inulin (Ross et al., 1973).
For ATP determination, liver and kidney were quick-frozen in a modified Wollenberger clamp (Wollenberger, Ristau & Schoffa, 1960) and extracted as described by Nishiitsutsuji-Uwo et al. (1967). Lactate, pyruvate, glucose and urea were determined by standard enzyme assays (Bergmeyer, 1974). ATP was determined by enzyme assays with hexokinase (EC 2.7.1.1) and by the luciferin/luciferase method (Stanley & Williams, 1969). There was close agreement for values obtained from the two methods. Sodium and potassium were measured on a flame photometer (IL 343) and carboxyl-\(^{14}\)C-labelled inulin (Radiochemicals, Amersham, Bucks., U.K.) radioactivity was counted in a Wacker scintillation counter. Inulin clearance, glomerular filtration rate and sodium reabsorption were calculated as previously described (Ross et al., 1973).

**Experimental procedure**

Tubules were prepared from a control and an injected animal and incubations were then carried out in parallel. Each of the procedures was tested separately for any effect on glucose synthesis in liver cells or tubules; injection of NaOH, HCl or exposure to ether were without effect and control values presented refer to animals which were not so treated. In experiments to determine the effect of added agents, tubules from single animals were incubated with or without the inhibitor.

**Statistics**

Comparisons were made by \(t\)-test; results are presented as mean ± SEM (\(n = \) number of observations). When tubules or liver cells prepared from a single animal were exposed to different treatments, paired tests were applied.

**Results**

**Isolated renal cortical tubules**

The rate of gluconeogenesis from lactate and pyruvate (Table 1) was significantly reduced (\(P < 0.001\)) by tubules prepared either 5 min or 60 min after intravenous injection of \(p\)-aminophenol (3 mmol/kg). The reduction varied from 35 to 90% with an average of 50% of control values. Gluconeogenesis from other substrates was also inhibited in tubules prepared from animals 5 min after intravenous injection of \(p\)-aminophenol: fumarate (control 98 ± 14-8 vs 42 ± 14-8), glutamine (control 104 ± 6-0 vs 33 ± 5-5), glycerol (control 92 ± 5-7 vs 42 ± 5-4) or fructose (control 193 ± 16-4 vs 91 ± 15-7). All substrates were added at 10 mmol/l, and tested

<table>
<thead>
<tr>
<th>Compound injected</th>
<th>Time (min)</th>
<th>Rate of glucose formation (µmol h(^{-1}) g(^{-1}) dry wt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lactate                                              Pyruvate</td>
</tr>
<tr>
<td>None</td>
<td>—</td>
<td>200-2±6.1 (49)                                               243-2±6.9 (49)</td>
</tr>
<tr>
<td>(p)-Aminophenol</td>
<td>5</td>
<td>131-4±16-7* (14)                                             112-2±21-2* (12)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>97-7±21-1* (10)                                             97-3±23-0* (10)</td>
</tr>
<tr>
<td>(N)-Acetyl-(p)-aminophenol</td>
<td>60</td>
<td>195-1±4-2* (14)                                             233-1±11-0 (11)</td>
</tr>
<tr>
<td>(paracetamol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p)-Phenacetidine</td>
<td>60</td>
<td>180-8±4-9* (4)                                              217-8±5-9 (4)</td>
</tr>
<tr>
<td>Phanazone</td>
<td>60</td>
<td>165-9±1-6* (4)                                              210-0±14-2 (4)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>60</td>
<td>169-5±12-7 (16)                                             210-8±16-7 (16)</td>
</tr>
</tbody>
</table>

* Significant difference from control value (\(P < 0.001\)).
in four pairs of animals. These differences were all highly significant ($P<0.01$). There was no such reduction after aspirin, phenazone, $p$-phenetidine or paracetamol given intravenously in similar doses even though one of these drugs, $p$-phenetidine, produced intense methaemoglobinemia. The apparently lower values for glucose synthesis in experiments with phenazone and aspirin (Table 1) did not differ from control studies on the same day.

Aspirin and paracetamol added directly to renal tubule preparations from control rats consistently reduced gluconeogenesis from both pyruvate and lactate by 20–30% (Table 2). $p$-Aminophenol added to renal tubule preparations interfered with the hexokinase assay for glucose, and so this effect was not further examined.

### Liver cells

In order to demonstrate that $p$-aminophenol was primarily nephrotoxic, the effect of this compound and some related compounds was examined in isolated liver cells. There was no reduction in the rate of glucose synthesis from lactate by isolated liver cells prepared 1 h after intravenous $p$-aminophenol (3 mmol/kg), but gluconeogenesis from pyruvate and alanine was reduced. Paracetamol injected intravenously (3 mmol/kg) also produced significant inhibition of glucose synthesis from pyruvate and alanine ($P<0.05$) but not from lactate, but the results were variable (Table 3). When paracetamol (4 mmol/l) was added to normal liver cell suspensions, gluconeogenesis from each sub-

### Table 2. Inhibition of gluconeogenesis in renal tubules by added aspirin or paracetamol

Renal cortical tubules prepared from starved rats were incubated in the presence of either aspirin or paracetamol at the concentrations indicated below. Substrates were added at a concentration of 10 mmol/l. Results for glucose synthesis are expressed as mean±SEM (with number of flasks in parentheses). $P$ values refer to paired t-test.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Substrate</th>
<th>Concentration (mmol/l)</th>
<th>Rate of glucose formation (μmol h⁻¹ g⁻¹ dry wt.)</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$-Acetyl-$p$-aminophenol</td>
<td>Lactate</td>
<td>Nil</td>
<td>140±10±5 (6)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>116±9±9±1 (6)</td>
<td>16±5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>107±7±8±6 (6)</td>
<td>23±0*</td>
</tr>
<tr>
<td></td>
<td>Pyruvate</td>
<td>Nil</td>
<td>199±7±15±0 (6)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>178±9±13±8 (6)</td>
<td>10±0*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>151±4±16±3 (6)</td>
<td>24±0*</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Lactate</td>
<td>Nil</td>
<td>174±8±9±6 (8)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>140±5±8±8 (8)</td>
<td>19±5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>132±5±11±8 (8)</td>
<td>24±0*</td>
</tr>
<tr>
<td></td>
<td>Pyruvate</td>
<td>Nil</td>
<td>229±1±11±3 (8)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>191±3±10±4 (8)</td>
<td>14±0*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>172±2±12±6 (8)</td>
<td>25±0**</td>
</tr>
</tbody>
</table>

* $P<0.05$; ** $P<0.01$.

### Table 3. Gluconeogenesis in liver cells prepared from rats injected with $p$-aminophenol or paracetamol

$p$-Aminophenol or $N$-acetyl-$p$-aminophenol (paracetamol) was injected intravenously as described. Liver cells were prepared at 60 min after injection, and from uninjected animals as control. Cells were incubated with the substrates indicated for 60 min, and the rate of glucose formation for the period 30–60 min was linear (see Krebs et al., 1973). Results are presented for the rate of glucose formation (30–60 min) and expressed as μmol of glucose h⁻¹ g⁻¹ dry weight (mean±SEM with number of flasks in parentheses). N.S. = not significant.

<table>
<thead>
<tr>
<th>Substrate (10 mmol/l)</th>
<th>Glucose formed (μmol h⁻¹ g⁻¹ dry wt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>L-Lactate</td>
<td>168±9±14±6 (12)</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>173±2±6±2 (10)</td>
</tr>
<tr>
<td>Alanine</td>
<td>101±5±10±9 (12)</td>
</tr>
</tbody>
</table>
strate tested was inhibited. Substrates were added at a concentration of 10 mmol/l, and tested in liver cells from four rats; glucose formation, expressed as μmol h⁻¹ g⁻¹ dry weight, was from lactate 158 ± 12 vs 82 ± 7, pyruvate 164 ± 14 vs 119 ± 8, glycerol 102 ± 7 vs 68 ± 9, alanine 79 ± 12 vs 40 ± 6 and fructose 160 ± 28 vs 118 ± 6. With the exception of the inhibition from fructose, these differences were significant (P < 0.05). Gluconeogenesis from lactate (10 mmol/l) was inhibited by 30% by concentrations of paracetamol as low as 0.5 mmol/l, and progressively inhibited by increasing concentrations of paracetamol. With paracetamol at 4 mmol/l, glucose synthesis from lactate fell from 142 ± 12.5 μmol h⁻¹ g⁻¹ dry weight to 79.6 ± 5.3 (n = 10), a highly significant difference (P < 0.001).

Isolated perfused kidney

When p-aminophenol was injected intravenously in rats (3 mmol/kg) 1 h before perfusion, flow rate and pressure were not altered but there was significant reduction of inulin clearance and sodium reabsorption (P < 0.001) in kidneys perfused with either glucose or lactate as substrate (Table 4). The significant reduction in total tubular sodium reabsorption to only 2% of the control value was accompanied by much smaller effects on glucose and lactate metabolism. In contrast with the marked inhibition in isolated tubules the rate of gluconeogenesis from lactate was normal in three out of six perfusions, but was reduced by 20, 40 and 50% in the remainder. The rate of lactate production from glucose was increased in four out of six perfusions. The ATP content of kidney was invariably reduced. When the kidney was prepared for perfusion only 5 min after intravenous injection of p-aminophenol, normal values for glomerular filtration rate and sodium reabsorption were obtained.

Liver and kidney ATP content in vivo

The ATP content of kidneys freeze-clamped in vivo was 8.4 ± 1.0 (n = 11) μmol/g dry weight. Five minutes after intravenous injection of p-aminophenol ATP content remained normal (11.0 ± 0.9, n = 7), but it was significantly reduced to 4.0 ± 0.5 (n = 10) (P < 0.01) 1 h after injection. ATP content of liver (9.4 ± 1.1; n = 11) was unaffected by injection of p-aminophenol. Paracetamol given intravenously was without effect on ATP content either in kidney (11.9; n = 2) or liver (10.3; n = 2).

Discussion

Our studies demonstrate an effect of p-aminophenol on the proximal convoluted tubule of the kidney. Gluconeogenesis is restricted to the cortex and has recently been localized to the cells of the proximal convoluted tubule (Schmidt & Guder, 1976). Substrates were selected (Krebs, 1964) to detect any inhibition of known rate-limiting enzymes of gluconeogenesis. Since p-aminophenol inhibited gluconeogenesis equally from all the substrates tested, it is unlikely that a specific enzyme in the pathway is the site of action of the compound or of its metabolite. The reduction in ATP content of the whole kidney 1 h after p-aminophenol might explain this observation since ATP is required for maximum rates of gluconeogenesis. The time taken to prepare isolated renal tubules, and for incubation with substrate, prevents measurement of gluconeogenesis at 5 min when amounts of ATP are still normal. The effects of intravenous p-aminophenol on the metabolism of isolated liver cells were different from those in isolated renal tubules. The maximum rate of gluconeogenesis from lactate was unaffected and hepatic ATP content was unchanged.

The dramatic abolition of Na⁺ transport in the perfused kidney within 1 h of intravenous p-aminophenol is also consistent with severe damage to the proximal tubule. It is unlikely to arise directly from inhibition of gluconeogenesis, since other inhibitors of gluconeogenesis are known to be without effect on Na⁺ reabsorption (Ross, Frega & Leaf, 1975; Ross & Bullock, 1976), but may result from the low tissue ATP content, especially in the proximal tubule. Impaired oxidative metabolism is suggested by an increased rate of lactate production from glucose. The reduction in glomerular filtration rate is more difficult to explain. A significant glomerular morphological lesion is not found at any time after intravenous p-aminophenol (Green et al., 1969; Funder et al., 1972). Moreover, in the perfused kidney, flow rate of medium (plasma flow) was constant and the reduction of glomerular filtration rate and Na⁺
Table 4. Effect of p-aminophenol on metabolic and physiological functions of the perfused rat kidney

Rats injected with p-aminophenol (see the Methods section) were prepared for kidney perfusion 5 or 60 min later. Kidneys were perfused for 60 min with either sodium L-lactate (10 mmol/l) or D-glucose (5 mmol/l) in the perfusing medium. Results of physiological function are expressed per kidney (mean wet weight 1.30 g). Mean values ± SEM (with number of results in parentheses) are shown.

<table>
<thead>
<tr>
<th>Time after injection (min)</th>
<th>Glucose</th>
<th>Lactate</th>
<th>Control</th>
<th>Glucose</th>
<th>Lactate</th>
<th>Rate of metabolism (nmol h⁻¹ g⁻¹ dry wt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inulin ratio (urine/plasma)</td>
<td>Glomerular filtration rate (ml/min)</td>
<td>Fractional Na⁺ reabsorption (%)</td>
<td>ATP (umol/g dry wt.)</td>
<td>Lactate formed from glucose (umol/g dry wt.)</td>
<td>Glucose formed from lactate (umol/g dry wt.)</td>
</tr>
<tr>
<td>5</td>
<td>31.2±18.2 (2)</td>
<td>0.52</td>
<td>0.012±0.004 (6)</td>
<td>32.8±6.2 (2)</td>
<td>0.019±0.011 (5)</td>
<td>96.3 (2)</td>
</tr>
<tr>
<td>60</td>
<td>1.4±0.17 (6)</td>
<td>0.012±0.004 (6)</td>
<td>32.4±12.0 (5)</td>
<td>94.3±2.0 (5)</td>
<td>72.6±7.1 (6)</td>
<td>72.4±2.5 (6)</td>
</tr>
<tr>
<td>Not perfused</td>
<td>19±1.0 (6)</td>
<td>0.012±0.004 (6)</td>
<td>91.8±2.0 (6)</td>
<td>9.3±0.022 (4)</td>
<td>9.3±0.022 (4)</td>
<td>9.3±0.022 (4)</td>
</tr>
<tr>
<td></td>
<td>15±1.0 (6)</td>
<td>0.012±0.004 (6)</td>
<td>91.8±2.0 (6)</td>
<td>9.3±0.022 (4)</td>
<td>9.3±0.022 (4)</td>
<td>9.3±0.022 (4)</td>
</tr>
</tbody>
</table>

* Not significantly different from control; ** P<0.05.
The effects of p-aminophenol upon the kidney and liver are observed after intravenous injection; in this respect p-aminophenol differs from aspirin, which affects gluconeogenesis only when added directly to renal tubule suspensions. Aspirin inhibition of glucose synthesis from lactate, pyruvate or other substrate (Dawson, 1975) is minor, and comparable with that seen with salicylate (2 mmol/l) in the isolated perfused rat liver (Woods, Stubbs, Johnson & Alberti, 1974). The effect on liver is not associated with morphological changes.

The effects of p-aminophenol are very different from those of paracetamol. Overdoses and high experimental doses of paracetamol produce liver necrosis (Dixon et al., 1971) and this has been related to the formation of a highly active toxic metabolite, which, after glutathione depletion, binds to liver cell thiol groups (Gillette, 1974). In the present experiments gluconeogenesis by isolated liver cells was depressed by paracetamol added in concentrations as low as 0.5 mmol/l. This may suggest a hepatotoxic effect separate from that described by Gillette (1974). Record, Iles, Cohen & Williams (1976) report lactic acidosis as a late effect of paracetamol in man, which is consistent with inhibition of hepatic gluconeogenesis.

The inhibition of gluconeogenesis induced by p-aminophenol in isolated renal tubules preceded severe tubular necrosis (Green et al., 1969), and is a further manifestation of its organ selectivity. C. A. Crowe, I. C. Calder, N. P. Madsen, C. C. Funder, C. R. Green, K. N. Ham & J. D. Tange (unpublished work) have shown that inhibition of mitochondrial respiration, oxidative phosphorylation and adenine triphosphatase activity could be procured by p-aminophenol administered in vivo. Cytochrome b5, cytochrome P450 and cytochrome c reductase are all reduced in the kidney, but not in the liver, by p-aminophenol (Crowe, Calder, Madsen, Funder, Green, Ham & Tange, 1977) and we have shown there is decrease in kidney ATP but no effect on liver ATP.

Renal damage is clearly associated with abuse of analgesic preparations containing phenacetin, and there is consequently a strong presumption that in some way phenacetin produced renal damage. It is this presumption which gives a wider significance to the nephrotoxic effects of p-aminophenol. The nephrotoxicity of aminophenolic compounds can be related to their chemical structure (Calder, Williams, Woods, Funder, Green, Ham & Tange, 1975) and compounds like p-aminophenol display nephrotoxicity. This does not imply that p-aminophenol itself is the nephrotoxic metabolite of phenacetin; but if excessive and prolonged dosage of phenacetin does produce renal damage, it is likely to do so by formation of some transient active metabolite similar to p-aminophenol.

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