Effect of acute paracetamol overdose on changes in serum and urine electrolytes

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What is already known about this subject

- Paracetamol causes renal failure in overdose. Experimental studies have shown that paracetamol can inhibit COX II systemically in a manner similar to selective COX-II inhibitors.
- In overdose nonsteroidal anti-inflammatory drugs such as ibuprofen, cause dose-dependent increase in urinary potassium excretion (FeK) and sodium retention, probably due to vasoconstriction.

What this study adds

- Paracetamol overdose is associated with dose-related hypokalaemia and kaliuresis of short duration (<24 h), suggesting a specific renal effect of paracetamol in overdose.
- This effect seems likely to be via cyclo-oxygenase inhibition and may be separate from the nephrotoxic effects of paracetamol.

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Keywords

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Aims

To investigate the effects of acute paracetamol overdose on renal function, serum and urine electrolyte excretion in man.

Methods

Two studies were performed in patients admitted with paracetamol overdose: a retrospective study examining changes in serum electrolytes, and a prospective study evaluating changes in serum and urine electrolytes. A control group with SSRI overdose was included in the prospective study.

Results

There was a significant dose-dependent relationship between admission (4 h) paracetamol concentration and fall in serum potassium in the retrospective study ($P < 0.01$) and a significant positive relationship between serum paracetamol at 4 h and fractional excretion of potassium at 12 h postingestion ($P < 0.01$) in the prospective study. No changes were seen in the control group. No cases developed renal failure.

Conclusions

Paracetamol overdose is associated with dose-related hypokalaemia, and kaliuresis of short duration (<24 h), suggesting a specific renal effect of paracetamol in overdose perhaps via cyclo-oxygenase inhibition. This effect seems distinct from any nephrotoxic effect of paracetamol.

Introduction

Paracetamol (acetaminophen) is the most commonly taken drug in overdose in the UK and US [1]. It is used frequently as an over-the-counter analgesic and antipyretic for minor aches and pains. It has been suggested that the analgesic and antipyretic effects of paracetamol are due to selective inhibition of COX-III, a variant of COX-I resulting in central inhibition of prostaglandin synthesis [2], whereas, in contrast to NSAIDs, paracetamol does not have an anti-inflammatory effect due to lack of peripheral inhibition of prostaglandin synthesis [3]. However, there is some *in vivo* evidence showing that, in addition to its CNS inhibitory effects on COX III, paracetamol can inhibit COX II systemically in a manner similar to the selective COX-II inhibitors [4].

Renal prostaglandin production is mediated primarily by cyclo-oxygenase, and plays a major role in compensatory renal haemodynamics. NSAIDs, and potentially paracetamol in overdose, have a variety of effects on the kidney. Severe adverse renal effects may partly be due to vasoconstriction consequent upon inhibition of renal prostaglandin-mediated vasodilatation, decreasing renal blood flow, and resulting in a reduction in glomerular filtration rate [5]. NSAID-induced renal failure depends on the drug, dose, duration of pharmacologic effect, and the health of the patient. Generally, individuals who are well hydrated and have normal renal function are unlikely to develop acute renal failure [6].

Paracetamol in overdose can cause renal failure. Most cases of renal failure have been reported to be in association with liver failure. However, isolated renal failure in the absence of liver damage has been reported [7]. Whether or not this is due to a direct nephrotoxic effect of paracetamol or is secondary to hepatic failure is not fully known. The overall incidence of paracetamol-induced renal failure has been reported to be less than 2%, but it reaches 10% in severely poisoned patients [8]. The incidence of renal failure without liver failure after paracetamol overdose is not known. The actual mechanism of nephrotoxicity in man is not fully understood. Direct tubular toxicity is one proposed mechanism. In studies on animals with high levels of renal microsomal P-450 activity, a single, nonlethal dose of paracetamol caused proximal convoluted tubular necrosis, possibly as a result of enhanced local production of the toxic quinoneimine intermediate metabolite [9, 10]. Other studies have reported elevation of blood urea nitrogen and serum creatinine after a toxic dose of paracetamol [11].

There is also a possibility that at high doses paracetamol-induced nephrotoxicity may be due to local haemodynamic changes, perhaps through COX inhibi-

tory effects in the kidney similar to classical NSAIDs. It has previously been shown, in a study on Wistar rats, that single doses of paracetamol caused a significant impairment in glomerular filtration rate and renal blood flow in a dose dependent manner [12]. This caused an alteration in tubular function, mainly in the distal tubules, observed as alteration in renal concentrating ability. The maximum changes were observed at 16 h postingestion, and after 24 h renal function was restored. The authors suggest that the early stage of paracetamol-induced nephrotoxicity might be due to vasoconstriction. Other work has shown phosphaturia after paracetamol overdose, possibly due to tubular effects of paracetamol in overdose [13, 14]. However, studies on therapeutic doses of paracetamol have found no effect on serum electrolytes [3, 15].

It has previously been shown that, in overdose, NSAIDs, such as ibuprofen, increase fractional excretion of potassium and cause sodium retention [16], an effect that might be due to renal vasoconstriction and consequent activation of the renin-angiotensin-aldosterone system.

We hypothesized that paracetamol in overdose might cause similar tubular effects to NSAIDs via inhibition of prostaglandin synthesis, vasoconstriction and activation of renin-angiotensin-aldosterone system causing electrolyte changes. To investigate the effect of paracetamol overdose on serum electrolytes and the utility of urine electrolytes in the early detection of renal dysfunction, we performed two separate studies, retrospective and prospective. In the retrospective study we explored the effect of paracetamol overdose on serum electrolytes and in the prospective study we investigated the effect of paracetamol overdose on serum and urine electrolytes.

Methods

For both the retrospective and prospective study, patients, male and female, aged between 16 and 64 years presenting with an overdose of paracetamol and admitted to the toxicology ward of the Royal Infirmary of Edinburgh were included. The period of the retrospective study was 2002–05 and the prospective study was conducted from 2004–06. Subjects in the prospective study were not included in the retrospective study.

For the retrospective study case notes of patients presenting within approximately 4–6 h of a stated ingestion of paracetamol were reviewed. Patients ingesting drugs known to be nephrotoxic, especially NSAIDs were excluded. Co-ingestion of benzodiazepines and or ethanol with paracetamol were included, as these compounds are not thought to be nephrotoxic. Records of patients who had at least two blood tests at 4–6 h

and 12–24 h postingestion were extracted and examined to exclude later presentations to the hospital (after 4–6 h postingestion), mixed overdose, pregnancy, and chronic underlying diseases, including history of kidney disease, liver disease, heart disease, hypertension and diabetes. Patients who were on regular prescribed potentially nephrotoxic drugs according to the British National Formulary [17] were also excluded.

In the prospective study similar exclusion criteria were used, but in addition patients with only paracetamol, or paracetamol with ethanol overdose were included. We also studied patients with single overdose of fluoxetine or paroxetine (SSRI: selective serotonin reuptake inhibitors) overdose according to the patient's history as a control group.

Information regarding time of ingestion, time of presentation to the hospital, medical history, drug history, antidote treatment with N-acetylcysteine (NAC) and vomiting was obtained from patient notes in the retrospective study and by interview and notes review in the prospective study.

The study was approved by the local Ethics Committee, and informed consent was obtained on admission. At 4 h after ingestion of the drug, routine blood and a paired urine sample were collected. Blood pressure and pulse rate were documented routinely to exclude haemodynamic compromise as a cause of renal dysfunction. Further blood and urine samples were taken at 12 h and at 24 h postingestion.

Analysis

In the retrospective study the biochemistry results of blood samples on admission (4–6 h postingestion) and 12–24 h postingestion (serum paracetamol, creatinine, sodium (Na), potassium (K), and bicarbonate (HCO_3) were extracted from the hospital computerized laboratory results system. The relationships between changes in serum electrolytes and serum paracetamol concentration at admission '4 h concentration' were examined.

In the prospective study, serum paracetamol, and plasma and urine creatinine, osmolality, Na, K, phosphate (PO_4) in blood and urine were measured in the Clinical Biochemistry Laboratories of the Royal Infirmary of Edinburgh. Transtubular potassium gradient (TTKG) was calculated from urinary/serum K concentration $\times$ serum/urine osmolality. Fractional excretion (Fe) was calculated for Na, K, and PO_4 from urinary/serum concentration of electrolyte $\times$ serum/urinary concentration of creatinine. Renal threshold of phosphate concentration (TmP/GFR : the ratio of the maximum rate of renal tubular phosphate reabsorption to the glomeru-

lar filtration) was calculated based on an established nomogram [18].

The relationships between serum paracetamol concentration at admission '4 h concentration' with changes in serum and urine electrolytes at 12 and 24 h postingestion were examined. The predictive value of urinary electrolytes in the early detection of a creatinine rise was also studied.

Since in the UK acetylcysteine (NAC) is differentially given to patients with specified 'risk factors' [17] in addition to a high serum paracetamol concentration, we grouped patients into three subgroups according to the serum paracetamol concentration at 4 h postingestion for illustrative purposes: group 1: patients with serum paracetamol concentrations less $<100 \text{ mg l}^{-1}$, group 2: patients with serum paracetamol concentrations between 100 and 199 mg l^{-1} , and group 3: patients with serum paracetamol concentrations 200 mg l^{-1} and above.

Statistical analysis

SPSS version 11.5 was used for statistical analysis. Data were tested for normality. Demographic data and two group comparisons (vomiting and alcohol ingestion) were compared using unpaired independent Student's *t*-test and Mann–Whitney U-test as appropriate. Multiple comparisons were made by one-way analysis of variance (ANOVA) with *posthoc* Bonferroni test comparison of groups for parametric and Kruskal–Wallis *H*-test with *posthoc* Dunn's multiple comparison tests for non-parametric analysis. A *P* value of <0.05 was considered as significant. Data are reported as mean $\pm$ standard error of the mean (SEM).

Results

In the retrospective study 155 patients with paracetamol overdose met our criteria. Thirty-eight % were male and 62% female. The patients had a mean age of 32.3 ± 2.6 years. There was a significant correlation ($r^2 = 0.10$, $P < 0.01$, $n = 155$, Figure 1) between admission serum paracetamol concentration and the change in serum potassium (mmol l^{-1}) between the admission and follow-up blood. The mean time between the two blood samples was $22.03 \pm 0.37 \text{ h}$. When patients were grouped according to admission serum paracetamol concentration, low: $<100 \text{ mg l}^{-1}$ (69.89 ± 4.43 , $n = 18$), medium: $100\text{--}199 \text{ mg l}^{-1}$ (145.98 ± 3.37 , $n = 69$), and high: $>200 \text{ mg l}^{-1}$ (283.31 ± 9.47 , $n = 68$), there was a significant difference in the change in serum potassium between groups with low and high (-0.08 ± 0.10 vs 0.50 ± 0.05 , $P < 0.01$, respectively) and medium and high (-0.31 ± 0.05 vs -0.5 ± 0.05 , $P < 0.05$, respectively) serum paracetamol concentration at admission.

Figure 1

Relationship between serum potassium change between admission (4 h) and follow-up serum K (mean time difference 22.03 ± 0.37 h) and serum paracetamol concentration at 4 h (retrospective study), $n = 155$, $r^2 = 0.10$, $P < 0.0001$

The mean reduction in serum potassium in the group with the highest paracetamol concentration (283 ± 9.47 mg l⁻¹) was -0.5 ± 0.05 mmol l⁻¹. If only patients receiving NAC were considered, the negative dose-dependent relationship between serum paracetamol at 4 h and serum potassium change remained ($r^2 = 0.06$, $P < 0.01$, $n = 139$, reduction in serum K from 3.86 ± 0.04 to 3.46 ± 0.03 mmol l⁻¹, $n = 139$).

In the prospective study, 41 cases of paracetamol overdose and 18 cases of SSRI overdose (16 fluoxetine and two paroxetine) completed the study. Not all patients complied fully with urine collection protocols, and the data reported relate to subjects completing a particular study component. There was no difference in either group with respect to age and gender. In both groups 39% were male and 61% female. In the paracetamol group mean age was 30.0 ± 1.9 years and in the control SSRI group 28.6 ± 2.6 years (Table 1).

In the paracetamol group, a kaliuresis occurred at 12 h. FeK and TTKG at 12 h postingestion were significantly correlated with serum paracetamol concentration at admission ($r^2 = 0.30$, $P < 0.01$ and $r^2 = 0.21$, $P < 0.01$, respectively). FeK and TTKG at 12 h were significantly different between groups with low and medium ($P < 0.01$ and $P < 0.05$, respectively), and between low and high serum paracetamol concentration at admission ($P < 0.01$ in both cases (Figures 2 and 3)). This change was no longer evident at 24 h. At 24 h, serum potassium was in a negative dose-dependent relationship with paracetamol concentration ($r^2 = 0.30$, $P < 0.01$, Figure 4).

No relationship was seen in the control SSRI group between stated dose of ingested drug and serum potas-

sium. The mean serum potassium change was significantly different between the paracetamol group and the control group at 12 h (-0.28 ± 0.05 mmol l⁻¹ vs -0.07 ± 0.08 mmol l⁻¹) (Table 1).

No effect on plasma or urinary electrolytes was seen in the SSRI (control) group. There was no relationship between ingested doses of SSRI and serum or urine electrolytes. Serum and urine electrolytes did not significantly change at different time points after ingestion.

There was consequently a significant difference between the paracetamol and SSRI group for urinary excretion of potassium at 4 h and serum potassium change at 12 h. The difference in FeK and serum potassium change had disappeared by 24 h (Table 1).

In both groups (paracetamol and SSRI) the ratio of urinary osmolality to plasma osmolality (U/P) was high at 4 h and 12 h. In the paracetamol group U/P osmolality was restored after 24 h. However, this continued increasing in the SSRI group (Table 1). There was no significant difference in serum and urinary excretion of potassium and phosphate at 4 h, 12 h and 24 h in the group with ($n = 31$) and without ($n = 10$) co-ingestion of alcohol.

There was a negative dose dependent correlation between serum paracetamol concentration and serum phosphate ($r^2 = 0.19$, $P < 0.01$) and renal threshold phosphate concentration (TmP/GFR) ($r^2 = 0.11$, $P < 0.05$) at 4 h (Figure 5). Serum phosphate and urinary excretion of phosphate did not change significantly at 12 h or 24 h postingestion.

In neither paracetamol study (retrospective and prospective) did vomiting affect serum potassium significantly. Additionally, in neither study was there a correlation between changes in serum bicarbonate and in serum potassium, or between serum bicarbonate and serum paracetamol concentration. There was no change in serum creatinine or serum sodium, in either of the paracetamol groups, or in fractional excretion of sodium in the prospective study. Only three cases in the paracetamol group developed features of liver injury (rise in ALT) at 24 h. Serum creatinine in these three cases was in the normal range. Blood pressure did not change significantly in either the paracetamol or control group.

Discussion

Understanding the processes by which paracetamol affects the kidney in overdose is key to any prediction of renal toxicity, and evaluation of potential antidotal therapy. Identification of patients at risk of renal failure would enable them to be targeted for special monitoring and intervention. Most cases of paracetamol intoxication seen in the UK are discharged within a 24 h time frame,

Table 1

Demographic characteristics of subjects and study variables (prospective study) (paracetamol and SSRI groups)

Variable	Groups	Number	Mean $\pm$ SEM	Significance level
Gender (F/M)	Paracetamol SSRI	25/16 11/7		NS
Age (years)	Paracetamol SSRI	41 18	30.04 $\pm$ 1.89 28.59 $\pm$ 2.63	NS
Change in serum K at 4–12 h (mmol l ⁻¹)	Paracetamol SSRI	37 18	-0.28 $\pm$ 0.05 -0.07 $\pm$ 0.08	$P < 0.01$
Change in serum K at 4–24 h (mmol l ⁻¹)	Paracetamol SSRI	31 10	-0.23 $\pm$ 0.09 -0.05 $\pm$ 0.18	NS
FeK at 4 h (%)	Paracetamol SSRI	41 18	16.06 $\pm$ 1.46 8.74 $\pm$ 1.43	$P < 0.01$
FeK at 12 h (%)	Paracetamol SSRI	34 16	16.47 $\pm$ 1.70 11.38 $\pm$ 1.80	$P = 0.05$
FeK at 24 h (%)	Paracetamol SSRI	31 9	7.35 $\pm$ 1.2 7.20 $\pm$ 1.48	NS
Plasma osmolality at 4 h (mosmol/Kg)	Paracetamol SSRI	40 17	300.08 $\pm$ 3.55 302.71 $\pm$ 3.91	NS
Plasma osmolality at 12 h (mosmol/Kg)	Paracetamol SSRI	37 18	290.24 $\pm$ 2.06 294.83 $\pm$ 2.76	NS
Plasma osmolality at 24 h (mosmol/Kg)	Paracetamol SSRI	32 10	287.69 $\pm$ 1.29 288.90 $\pm$ 1.62	NS
Urine osmolality at 4 h (mmol/Kg)	Paracetamol SSRI	41 18	600.12 $\pm$ 49.09 581.11 $\pm$ 65.81	NS
Urine osmolality at 12 h (mmol/Kg)	Paracetamol SSRI	34 17	659.94 $\pm$ 48.55 777.53 $\pm$ 68.99	NS
Urine osmolality at 24 h (mmol/Kg)	Paracetamol SSRI	31 9	462.26 $\pm$ 42.89 905.22 $\pm$ 42.80	$P < 0.01$

during which hepatic toxicity can be predicted, and appropriate treatment continued, or commenced. This is not the case for renal toxicity, which develops later. The true extent of renal toxicity is unknown, since only the most severe forms re-present as acute renal failure. According to our clinical experience of patients presenting to the Toxicology unit of the Royal Infirmary of Edinburgh one or two out of 1000 cases with paracetamol overdose may develop renal failure without significant liver involvement (rise in ALT).

The main finding of the retrospective study conducted here was the dose-dependent relationship between 4 h serum paracetamol concentration and fall in serum potassium. The prospective study demonstrated a relationship between 4 h serum paracetamol concentration and 24 h serum potassium and additionally showed an increase in FeK and TTKG at 12 h postingestion, again in a dose-dependent relationship with serum paracetamol, that had normalized by 24 h. These changes in potassium were not seen in the SSRI control group. Because no patients studied developed a significant rise in creatinine, we are unable to say if our findings are relevant to the development of nephrotoxicity. However,

the results of our retrospective and prospective studies were consistent with the result of a previous pilot study on ibuprofen overdose, a classical NSAID, investigating the utility of excretion of potassium as a measure of ibuprofen toxicity, which also showed a dose-dependent relationship between dose of ibuprofen ingested and FeK [16].

The most common causes of hypokalaemia from renal potassium loss are due to either medication, endogenous hormone production or in rare cases, intrinsic renal defects [19]. The dose-dependent relationship between serum paracetamol concentration and FeK at 12 h postingestion suggests renal loss of potassium in paracetamol overdose. However, there were some confounding factors which might affect change in serum potassium.

Firstly hydration may have had an effect as the group of patients with high paracetamol concentrations received NAC in serum dextrose 5%. However, there was no significant change in serum sodium relating to NAC treatment in either study, or change in plasma osmolality in the prospective study indicating that it is very unlikely that hypokalaemia was a result of dilution.

Figure 2

Time course of FeK changes according to serum paracetamol concentration at 4 h (prospective study). Data shown by risk category (serum paracetamol < 100 mg l⁻¹ low, (□); 100–199 mg l⁻¹ medium, (▒); and >200 mg l⁻¹ high, (■)), in box and whisker format (Median, interquartile box). FeK at 12 h is significantly different between the groups with low and medium ($P < 0.01$) and low and high serum paracetamol ($P < 0.01$). Para Lev: serum paracetamol concentration. (Circle shows outliers which are cases with values between 1.5 and 3 box lengths from the upper and lower edge of the box. The box length is the interquartile range. Asterisk shows extremes which are cases with values more than 3 box lengths from the upper and lower edge of the box). N = number of subjects

Secondly, since only cases with a particular risk or high serum paracetamol concentrations received NAC infused in 5% dextrose, this may have altered serum potassium concentrations through endogenous insulin production induced by 5% dextrose, resulting in movement of potassium into the intracellular compartment, or NAC might have affected tubular potassium handling directly. To determine the effect of NAC and 5% dextrose on serum K and FeK, the ideal would be to compare these measurements in two groups with the same serum paracetamol concentration who did and did not receive NAC treatment. However, due to the unequal distribution of subjects in each group, we could not define such groups for comparison (Table 2). To address this in the retrospective study we examined the relationship between serum paracetamol at 4 h and serum potassium change between the two blood tests in the NAC treated group alone and found that the significant relationship seen in all subjects persisted. While this does not rule out an effect of NAC, it does suggest that serum

Figure 3

Time course of TTKG changes according to serum paracetamol concentration at 4 h (prospective study). Data shown by risk category (serum paracetamol < 100 mg l⁻¹ low, (□); 100–199 mg l⁻¹ medium, (▒); and >200 mg l⁻¹ high, (■)) in box and whisker format (Median, interquartile box). TTKG at 12 h is significantly different between groups with low and medium ($P < 0.05$) and low and high serum paracetamol ($P < 0.01$). Para Lev: serum paracetamol concentration. (Circle shows outliers which are cases with values between 1.5 and 3 box lengths from the upper and lower edge of the box. The box length is the interquartile range. Asterisk shows extremes which are cases with values more than 3 box lengths from the upper and lower edge of the box). N = number of subjects

paracetamol itself is a factor in serum K change. Further studies investigating the actual effect of NAC in 5% dextrose on renal function and electrolyte handling and serum K in healthy volunteers are required to define this further.

Thirdly, vomiting is known to cause hypokalaemia as a consequence of metabolic alkalosis. However, in neither retrospective nor prospective studies could we find an effect of vomiting. In addition, serum K and FeK did not show a relationship with serum bicarbonate which would be expected if vomiting was a factor.

A small number of patients had ingested alcohol before or with drug ($n = 10$), in the prospective study, with, thus, a potential effect of alcohol on serum K and FeK. An experimental study on rats investigating the acute effect of ethanol on renal electrolyte transport showed diuresis, an increase in FeNa and no change in FeK within 1 h after acute ingestion of ethanol [20]. Another animal experiment studying the acute effect of ethanol on renal haemodynamics and monovalent ion excretion over a longer period showed an increase in excretion of sodium at 2 h, 10 h, 18 h and 26 h

Figure 4

Relationship between serum potassium at 24 h and serum paracetamol concentration at 4 h (prospective study), $n = 31$, $r^2 = 0.29$, $P < 0.01$

Figure 5

Relationship between renal threshold phosphate concentration (TmP/GFR) and serum paracetamol concentration at 4 h (prospective study), $n = 38$, $r^2 = 0.11$, $P < 0.05$

	Number (NAC/ non-NAC treated)	Paracetamol in the NAC vs non-NAC treated group
<i>Retrospective study</i>		
Group 1	10/8	56.29 ± 8.29 vs 78.00 ± 3.29
Group 2	61/8	145.59 ± 3.54 vs 149.00 ± 11.60
Group 3	68/0	283.31 ± 9.46
<i>Prospective study</i>		
Group 1	3/13	88.33 ± 2.90 vs 55.08 ± 7.00
Group 2	14/4	143.57 ± 6.58 vs 132.00 ± 6.84
Group 3	7/0	286.57 ± 29.97

Table 2

Numbers of subjects in each group according to the serum paracetamol concentration (mg l^{-1}) at 4 h (retrospective and prospective studies) and NAC treatment

postingestion and a biphasic change in potassium excretion [21] while potassium excretion decreased at 2 h and started increasing at 10 h, 18 h and 26 h. The maximal change was seen at 18 h. In the current study, we did not measure serum alcohol concentration. However, we compared changes in serum and urine electrolytes in the groups with and without alcohol ingestion. The results of the current study did not show a significant difference in serum sodium and potassium, phosphate, FeNa, FeK and FePO₄ between these groups, suggesting that alcohol is unlikely to contribute to the observed changes in serum and urine electrolytes. Further studies in a larger group of subjects with measurements of serum alcohol concentrations could give us a better understanding of dose and time dependent effects of alcohol on electrolyte handling in paracetamol overdose.

Finally, paracetamol in aqueous solution has a pH of 6.24 [22]. While the buffering capacity of plasma is large, it is possible that a high serum paracetamol concentration is associated with a mild acidosis that resolves

as the paracetamol concentration falls. This would result in potassium shifts between the plasma and the intracellular compartment. However, we did not see any correlation between serum bicarbonate and paracetamol concentration. Additionally, acidosis would be associated with potassium efflux from the intracellular compartment, increasing serum potassium concentrations, the converse of the result observed in this study.

In a study on Wistar rats [12], the effect of different single doses of paracetamol on renal function and electrolytes handling was examined, and GFR and renal plasma flow was significantly decreased in a dose-dependent manner. The time course of changes in electrolyte excretion in the group given a toxic dose of paracetamol (1000 mg kg^{-1}) showed an increase in FeK and no change in FeNa at 1 h, 6 h, and 16 h. The maximal change in FeK and renal perfusion was at 16 h postingestion and was restored by 24 h. The authors suggested that early stages of paracetamol nephrotoxicity are due to renal haemodynamic changes. In the

current study, we did not directly measure renal blood flow, nor did creatinine change significantly, though this is a relatively insensitive marker of small changes in GFR. The major changes seen in this study were in potassium, with the maximum derangement in FeK occurring after 12 h and restored after 24 h which was consistent with the results of animal studies.

Aldosterone is the most important hormone regulating total body potassium homeostasis, causing hypokalaemia by stimulating potassium uptake into cells and increasing renal potassium excretion [19]. Aldosterone secretion is increased by renal hypoperfusion via activation of the renin-angiotensin-aldosterone axis. Our results could therefore be consistent with the early effects of paracetamol toxicity being due to renal haemodynamic change consequent upon activation of the renin-angiotensin-aldosterone axis, seen here as increasing potassium excretion. The lack of effect on sodium excretion suggest, in this study, where no patients developed significant renal dysfunction, that this effect is mild but studies in patients with more severe overdose would be of interest in this respect.

In the SSRI group an increase in urine osmolality at 4 h, 12 h and 24 h supports the results of previous studies [23–25], reporting hyponatraemia secondary to SSRI-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH). However, in our study serum sodium and FeNa did not change significantly.

The other result of the study was a negative dose-dependent relationship between serum paracetamol, serum phosphate and renal threshold phosphate concentration (TmP/GFR) at 4 h postingestion. This finding was consistent with the results of other studies investigating renal loss as a source of hypophosphataemia after paracetamol poisoning [13, 14]. A decrease in renal threshold phosphate concentration in the early stage of toxicity can thus be potentially used as an early marker in determining the severity of paracetamol toxicity.

Because no patients developed significant renal dysfunction we could not assess the utility of urinary excretion of electrolytes in predicting specific renal toxicity and studies in patients with this outcome are required.

We conclude that paracetamol overdose is associated with a reduction in serum potassium and kaliuresis, which is proportional to the dose ingested and is of relatively short duration, not longer than 24 h postingestion in this study. This suggests a specific renal effect of paracetamol in overdose. These findings might be consistent with increasing aldosterone action on the distal tubules as renal perfusion falls due to paracetamol-induced renal vasoconstriction consequent upon COX inhibition, and hence reduced production of vasodilator

prostaglandins. Measurement of aldosterone and plasma renin activity (PRA) in future studies may give us a better understanding of the renal effects of paracetamol overdose. None of the cases developed significant renal impairment. It is therefore unlikely that these effects are directly related to the renal failure seen occasionally in paracetamol overdose.

Limitation of the study

In the retrospective study due to the nature of the study we could not obtain the precise information from patients and we relied on the information recorded in the patient notes. As the study required having two sets of biochemistry tests in order to investigate the changes in serum electrolytes, we had to include those cases that had at least two sets of data. This would suggest that the subjects were not necessarily representative of the whole population, particularly at lower doses of paracetamol.

In the prospective study due to nature of the subjects not all cases were able to comply with all blood and urine collections. As routine drug screening for drugs of abuse would not have detected the presence of NSAIDs and since a complete screen of this nature would be extremely expensive, we did not do a drug screen to rule out co-ingestion of other drugs in the paracetamol group. We excluded cases of mixed overdose by patient interview. However, it would have been more likely for co-ingestion to confound and reduce the power of the data and statistical analysis rather than increase it giving us the positive result we have seen. The precise effect of 5% dextrose and NAC itself was not clear, but our intention was not primarily to examine this. The effects of paracetamol seen are independent of NAC administration.

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