REVIEW

Glue-Sniffing and Distal Renal Tubular Acidosis: Sticking to the Facts[1]

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ABSTRACT

An index case is presented to introduce the subject of the acid-base and electrolyte abnormalities resulting from toluene abuse. These include metabolic acidosis associated with a normal anion gap and excessive loss of sodium and potassium in the urine. The major question addressed is, what is the basis for the metabolic acidosis? Overproduction of hippuric acid resulting from the metabolism of toluene plays a more important role in the genesis of the metabolic acidosis than was previously believed. This conclusion is supported by the observation that the rate of excretion of ammonium was not low during metabolic acidosis in six of eight patients, suggesting that distal renal tubular acidosis was not an important acid-base abnormality in most cases where ammonium was measured. The excretion of hippurate in the urine unmatched by ammonium also mandates an enhanced rate of excretion of the cations, sodium and potassium. The loss of sodium causes extracellular fluid volume contraction and a fall in the glomerular filtration rate, which may transform the normal anion gap type of metabolic acidosis into one with a high anion gap (accumulation of hippurate and other anions). Continuing loss of potassium in the urine leads to hypokalemia. An understanding of the metabolism of toluene provides the basis for the unusual biochemical abnormalities seen with abuse of this solvent.

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The association between toluene and a normal anion gap type of metabolic acidosis was first recognized by Taher *et al.* (1). The basis for this acidosis was said to be distal renal tubular acidosis (RTA) (1–12). These reports have, however, largely underestimated the organic acid load resulting from the metabolism of toluene and have focused on less reliable criteria for this diagnosis (urine pH versus the rate of excretion of ammonium [NH_4^+]). The purpose of this review is to reexamine the potential causes for the metabolic acidosis associated with toluene abuse and to emphasize the importance of this acid load. An index case which led to this analysis is summarized below. Two aspects which suggested that the rate of excretion of ammonium (NH_4^+) was not low will be emphasized.

INDEX CASE

A 32-year-old female of North American Indian descent was brought to the hospital after being found semiconscious in her home. She had a long history of solvent abuse, and her current illness was the result of recent glue-sniffing. On examination, the blood pressure was 140/80 mm Hg and the pulse rate was 80/min in the supine position; on standing, the blood pressure fell to 120/70 and the heart rate increased to 90/min. The jugular venous pressure was below the sternal angle. There was evidence of cerebellar dysfunction (chronic), attributed to the long-term abuse of toluene. No other specific findings were evident. Results of laboratory investigations are shown in Table 1. Toxic screen was negative. After catheterization of the bladder, her urine output was 0.5 liters in the first hour.

Comments

This patient presented with severe hypokalemia and metabolic acidosis with a normal anion gap. Given a concentration of potassium (K) in the plasma of 1.9 mmol/L, the concentration of K in the urine was inappropriately high, with a tubular fluid:

TABLE 1. Laboratory values on admission in the index case[a]

Plasma	
Na (mmol/L)	139
K (mmol/L)	1.9
Cl (mmol/L)	108
HCO_3 (mmol/L)	15
Glucose (mmol/L)	5.5
Urea (mmol/L)	0.5 (1.4 mg/dL)
Creatinine (μmol/L)	84 (1.0 mg/dL)
Anion gap (mEq/L)	18
pH	7.33
Urine	
Na (mmol/L)	15
K (mmol/L)	17
Cl (mmol/L)	N/A
Osmolality (mosmol/kg of H_2O)	180
pH	5.0

[a] For details, see the text. The anion gap was calculated as (Na + K) − (Cl + HCO_3).

plasma K ratio of at least 8 (13).

The osmolality of the urine was surprisingly low in view of the concurrent extracellular fluid (ECF) volume contraction. In another way, however, the osmolality of the urine was too high. We could only account for about 70 of the 180 mosmol/kg of H_2O by using the formula, urine osmolality = 2(Na + K) + urea + glucose, all in mmol/l units. This calculation was made as follows: first, there was no glycosuria; second, the concentration of urea in the urine must be small in this case; it can be estimated as follows. If as much as 75 mmol of urea was filtered per day (glomerular filtration rate [GFR] × $[urea]_{plasma}$, 150 liters/day × 0.5 mmol/L), the excretion of urea could be no more than 75 mmol/day or 3 mmol/h (an overestimate, as there is reabsorption of urea). Because the volume of urine collected over the hour period in the emergency room was 0.5 liters (may be inaccurate representation of true production of urine as residual urine might have been present in the bladder), the maximum calculated concentration of urea is <10 mmol/L. The urine osmolality is therefore 2(15+17) + 6 + 0, or 70 mosmol/kg of H_2O, and the osmolal gap was 110 mosmol/kg of H_2O. In the absence of other osmolytes, this suggests a high rate of excretion of NH_4^+ (14). Metabolites of toluene (hippurate) might well account for most of the remainder of this osmolal gap.

There is another indirect clue that the urine might contain an appreciable quantity of NH_4^+ in this case. The concentration of urea in the plasma was exceedingly low given the degree of contraction of the ECF volume (0.5 mmol/L or 1.4 mg/dL). This might reflect two processes, a low intake of protein and excretion of nitrogenous wastes as NH_4^+ and hippurate rather than urea.

Because this case captured our attention, but raised more questions than it answered, a detailed search of the literature was undertaken.

REVIEW OF THE LITERATURE

Reports of cases with toluene abuse were included in this review. Studies were identified by means of a computer-assisted literature search of the National Library of Medicine data base by using the key words "toluene" and "renal tubular acidosis." The reference list of each paper was checked for further papers on this subject.

Fourteen papers were identified, giving details on 57 patients representing 78 episodes of toluene abuse (1–12,15,16). The mean age of the patients was 25 ± 5 years, and the male:female ratio was 1:1.6.

Metabolic acidosis was observed in 59 of 68 episodes. In 46 episodes, the metabolic acidosis was associated with a normal anion gap in the plasma, and in 13 episodes with an increase in the anion gap. We have compared the laboratory data according to whether a wide anion gap (>20 mEq/L) was present or not (Table 2). It should be pointed out that in a few cases, a mixed type of metabolic acidosis was present. The presence of an increased anion gap in the plasma was associated with a lower concentration of Na and bicarbonate in the plasma, a lower blood pH, and a higher concentration of creatinine in the plasma. One possible explanation may be that with a greater degree of ECF volume contraction induced by the obligatory excretion of sodium (Na) along with hippurate, prerenal failure ensued. This led to a fall in the rate of excretion of hippurate, resulting in an increase in the level of hippurate in plasma and an increase in the anion gap. Renal failure may also contribute to a lower rate of excretion of NH_4^+ despite the acid load, resulting in more severe metabolic acidosis.

A striking finding in this survey was the observation that six of eight patients studied immediately after presentation had rates of excretion of NH_4^+ in the presence of metabolic acidosis that were higher than expected if the cause of the metabolic acidosis was simply distal RTA (median, 88 μmol/min; Table 3) (1,7,10). In these patients with such a high rate of excretion of NH_4^+, the metabolic acidosis must have occurred on some basis other than that of a toluene-induced distal renal tubular acidosis.

METABOLISM OF TOLUENE

Toluene, a hydrophobic chemical, will accumulate in lipoidal structures (17) unless it can be excreted. During glue-sniffing, it is inhaled rather than being excreted via the lungs. After sniffing stops, toluene, a volatile compound, is cleared rapidly via the lungs (17).

TABLE 2. Comparison of patients with and without an increased anion gap after toluene abuse[a]

	Normal Anion Gap	Increased Anion Gap
Serum		
Na (mmol/L)	138 ± 3.5 (41)	131 ± 6.7 (10)*
K (mmol/L)	2.8 ± 1.0 (41)	3.1 ± 0.8 (10)
Cl (mmol/L)	115 ± 5.4 (41)	100 ± 11.8 (10)*
HCO_3 (mmol/L)	12 ± 4.9 (41)	4 ± 3.9 (10)*
Anion gap (mEq/L)	14 ± 3.0 (41)	31 ± 7.2 (10)*
BUN (mg/dL)	11 ± 5.8 (26)	18 ± 15.9 (9)†
Creatinine (mg/dL)	1.1 ± 0.5 (32)	3.7 ± 1.4 (10)*
Blood pH	7.2 ± 0.1 (36)	7.0 ± 0.1 (10)*
Urine pH	6.0 ± 0.6 (38)	5.4 ± 0.4 (9)*

[a] The laboratory values of 59 patients with metabolic acidosis due to toluene abuse were obtained from previous papers. The anion gap was calculated as (Na + K) − (Cl + HCO_3), the normal range being 16 ± 4. The data are presented as mean ± SD, and the number of patients with available data is given in parentheses. The patients were separated into two groups—those with a normal anion gap in the plasma (46) and those with an increased anion gap (13). A statistical comparison between the two groups (unpaired *t* test) showed that the patients with an increased anion gap had a lower concentration of sodium, chloride, and bicarbonate in the plasma and a higher concentration of blood urea nitrogen (BUN) and creatinine. * $P < 0.01$; † $P < 0.05$.

TABLE 3. Renal acidification during toluene-induced acidosis[a]

Patient No. (Ref. No.)	Plasma K (mmol/L)	Creatinine (mg/dL)	Anion Gap (mEq/L)	Blood pH	Urine pH	TA (μEq/min)	NH_4 (μEq/min)	NAE (μEq/min)
1 (10)	3.4	0.7	15	7.36	5.6	18.0	17.0	35.0
2 (10)	3.4	0.7	18	7.36	5.6	17.0	77.0	91.0
3 (10)	3.2	0.6	13	7.32	6.1	13.0	14.0	24.0
4 (10)	2.6	0.6	13	7.37	6.9	25.0	99.0	98.0
5 (10)	3.1	1.2	14	7.27	6.0	21.0	40.0	61.0
6 (7)	3.1	1.1	13	7.24	5.9	59.6	59.5	654.6
7 (7)	3.8	1.2	15	7.32	5.8	37.6	131.0	168.6
8 (1)	1.7	0.8	12	7.24	6.0	2.0–12.1	50–125	50.6–132.9

[a] The laboratory values of eight patients with metabolic acidosis due to toluene abuse and with available data on excretion of NH_4 are summarized. The rates of excretion of NH_4^+ were not low in six patients and therefore indicate that distal RTA was not present at this time. NAE, net acid excretion.

The conversion of toluene, the electroneutral methyl-benzene, to organic acids occurs in the liver (Figure 1). Toluene is metabolized by the cytochrome P-450 system, primarily in the cytoplasm of the liver (18,19). This metabolism generates a hydroxyl radical capable of reacting with other compounds and confers more water solubility; this product is benzyl alcohol. This inserted oxygen atom allows the cell to generate a carboxylic acid (benzoic acid) via alcohol and aldehyde dehydrogenases, akin to the formation of acetic acid from ethanol. Benzoic acid is an excellent substrate for conjugation (adding a glycine group) to form hippuric acid in hepatic mitochondria (Figure 1). The latter steps in this pathway have a high capacity. In fact, in patients with an inborn error of metabolism of the urea cycle, sodium benzoate may be administered to provide the means to excrete nitrogenous wastes in a form other than urea. To summarize, the formation of benzoic and hippuric acids adds one H^+ to the body for every toluene metabolized, thus generating an acid load that must be eliminated.

There are conflicting data regarding the rate of production of hippuric acid after exposure to toluene. On the one hand, exposure of normal subjects to the maximum permissible dose of toluene in the work place (200 ppm) for 8 h leads to only a very modest rate of excretion of hippurate (25 mmol) (20). On the other hand, many patients who abuse toluene have a very severe metabolic acidosis, implying that at least 500 mmol of acid was produced (21). Further, some of these patients have an extremely high concentration of hippurate in the urine on presentation (Table 4).

Examining the time course of hippuric acid excretion after a controlled exposure to toluene provides insights which might reconcile these two sets of data.

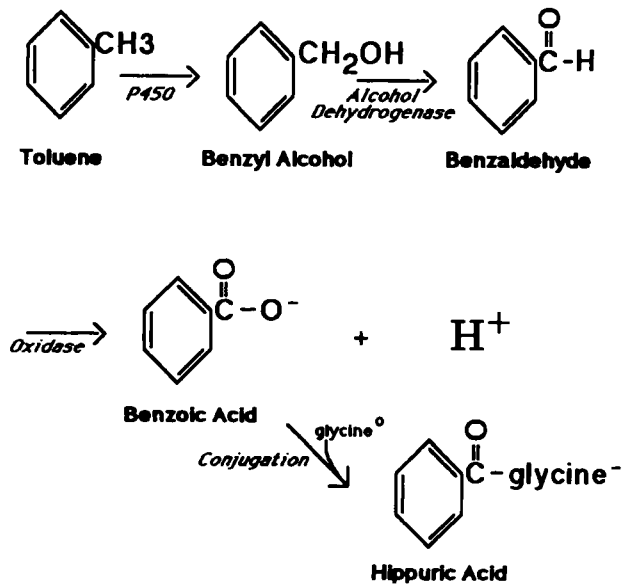

Figure 1. The metabolism of toluene. Toluene is metabolized in three steps to benzoic acid, thus generating an acid load which is added to the body. Conjugation of benzoate with the amino acid, glycine, results in the formation of hippurate. With adequate renal function, hippurate is excreted in the urine rapidly.

TABLE 4. Toluene and its metabolite (hippuric acid) determination

Patient No. (Ref. no.)	Blood Toluene (mmol/L)	Urine Hippuric Acid (mmol/L)
1 (10)	0.20	171.4
2 (10)	0.14	257.1
3 (10)	0.03	17.1
4 (11)	0.23	41.1

Two features of hippurate metabolism deserve emphasis. First, hippurate is excreted in the urine at an extremely rapid rate. It is removed from the circulation by the kidney by both filtration and secretion (22). Second, the excretion of the bulk of the hippurate occurs after a surprisingly long lag period (24 h after an exposure) (20). These observations, together with the fact that toluene is cleared from the blood very rapidly (within 70 min) by the lungs after exposure (17), imply that most of the hippuric acid is formed at a time when the level of toluene in the blood is very low. This suggests that the key enzyme in this sequence of reactions which form hippuric acid was activated or induced to a major extent; there is strong evidence to support this hypothesis (18,19). The implications of these observations for the severity of the metabolic acidosis are twofold. First, if the cytochrome P-450 which oxidizes toluene were already induced (before exposure to toluene, barbiturates, etc.), the rate of production of hippuric acid could be much higher. Second, the time for recovery from the acidosis could easily take several days and be even longer if the patient had a compromised rate of excretion of NH_4^+. This delay in recovery has been noted by Batlle *et al.* (10).

To summarize, patients who are exposed to toluene on a chronic basis have several features which, taken in combination, could help explain a more severe degree of metabolic acidosis. First, they are likely to be exposed to higher doses of toluene (many thousand parts per million) (23) and possibly for a longer duration. Second, repeated exposure to toluene could induce their cytochrome P-450. Third, if they are obese, more toluene could be "stored" in adipose tissue. Fourth, either the low GFR or interstitial disease of the kidney could diminish the rate of excretion of NH_4^+ in the urine.

The level of toluene in blood might be higher and that of hippuric acid lower if the rate of metabolism of toluene was reduced, either because of hepatic destruction (cirrhosis, hepatitis) or competitive inhibition of alcohol dehydrogenase by ethanol. Furthermore, those individuals who metabolize toluene more slowly because of low activities of cytochrome P-450 and/or alcohol dehydrogenase might have complications related to the accumulation of toluene or benzyl alcohol rather than hippuric acid. It is not at all clear which of these metabolites poses the greatest threat to the patient.

TOLUENE AND DISTAL RTA

Before discussing whether toluene causes distal RTA, it is important to clarify what the key features should be to make this diagnosis. First, the diagnosis of acidosis of renal origin is established by documenting the presence of hyperchloremic metabolic acidosis which is due to a low rate of excretion of net acid (24). Renal "tubular" acidosis implies that the major cause of the low rate of excretion of net acid is not a very low GFR. Some patients with RTA have a low rate of reabsorption of bicarbonate; they have proximal RTA.

One way to decide what the critical abnormality is in distal RTA is to examine why metabolic acidosis develops in this situation. Metabolic acidosis occurs when the rate of input of H^+ exceeds its removal. Since the rate of input of H^+ is not increased in patients with distal RTA, the lesion is a low rate of excretion of net acid. Bicarbonaturia is not an important component of this lesion; thus, there must be a reduction in the rate of excretion of titratable acid or NH_4^+. Because of the facts that the pH of the urine is usually 1 U lower than the pK′ of the principal buffer phosphate (6.75) (25) and that there is no major

decline in phosphaturia, the key lesion must be a low rate of excretion of NH_4^+. Indeed, this has been documented in patients with distal RTA (for a review, see reference 26).

Having recognized that distal RTA is really a "low NH_4^+ excretion disease," "what is the role of the urine pH in this diagnosis?" A pH of 5.0 in the urine represents too few free H^+ to be important (0.01 mmol/L). Therefore, the pH of the urine will be valuable only if it provides a reliable index of the rate of excretion of NH_4^+. We shall emphasize below that this pH is not a reliable way to monitor the rate of excretion of NH_4^+ during metabolic acidosis (Figure 2). Therefore, the focus of the diagnosis of distal RTA must be changed from the pH of the urine to the rate of excretion of NH_4^+ (26).

Toluene sniffing is generally accepted to be associated with a normal anion gap type of metabolic acidosis that is due to distal RTA, presumably as a result of a rate-dependent defect in distal nephron H^+ secretion. The evidence for these statements stems from the following observations: (*1*) the presence of metabolic acidosis with a normal anion gap; (*2*) an impaired ability to sustain a steep pH gradient in the collecting duct as deduced from the finding of a urine pH greater than 5.5 during metabolic acidosis; (*3*) the inability to increase the PCO_2 in a highly alkaline urine appropriately; and (*4*) a decreased rate of secretion of H^+ in turtle bladder exposed to toluene.

In the following paragraphs, we shall scrutinize each of the above, in an attempt to define the pathophysiology of the metabolic acidosis associated with toluene sniffing.

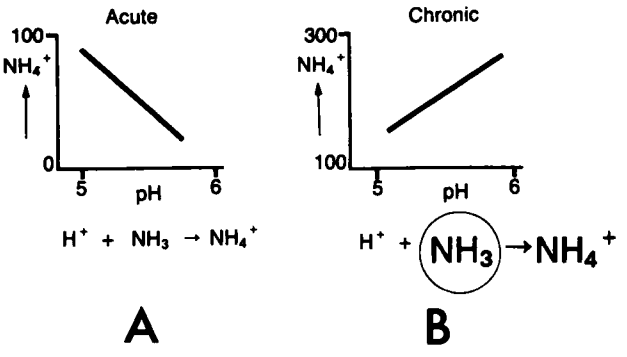

Figure 2. Effect of the urine pH on the excretion of NH_4^+. In acute acidosis (A), the rate of excretion of NH_4^+ is higher when the urine pH is lower. The main driving force is an increased rate of secretion of H^+. In chronic acidosis (B), the main driving force is an increase in NH_3 in the medullary interstitium due to augmented ammoniagenesis; this is relatively larger than the increment in H^+ secretion. Thus, the urine NH_4^+ excretion rate is increased in conjunction with a *higher* pH of the urine. Reproduced with the permission of the authors (43).

1. Normal Anion Gap Type of Metabolic Acidosis

Metabolic acidosis is traditionally divided into a wide or a normal anion gap subtypes (27–29). The former is largely the result of overproduction of acid, while the latter is the result of loss of sodium bicarbonate through the kidney (proximal RTA, acetazolamide) or the intestinal tract (diarrhea) or from failure of the kidney to generate "new" bicarbonate, i.e., distal RTA. The overproduction of acid type of metabolic acidosis, however, can present with a normal anion gap; this is illustrated in the following three steps (Figure 3): (*1*) production of an organic acid; (*2*) titration of these protons with endogenous bicarbonate to form CO_2, which is exhaled. The net result is loss of bicarbonate from the body; (*3*) excretion of the conjugate base of that acid in the urine at a rate which exceeds the rate of excretion of H^+ and NH_4^+; thus, it will be lost with Na or K.

Taken together, the above three steps will lead to an "indirect" loss of sodium bicarbonate; a metabolic acidosis due to overproduction of acid will be accompanied by a normal anion gap in the plasma. The maintenance of this normal anion gap in toluene abuse depends on the characteristics of toluene distribution and metabolism, and the near-complete elimination of hippurate in the urine. If the rate of excretion of hippurate falls below its rate of production, this anion will accumulate in the plasma, raising the anion gap. This could occur with a low GFR or inhibited secretion of hippurate in the kidney.

2. Distal RTA—The Problem with the Urine pH during Metabolic Acidosis

The second piece of information that led to the conclusion that toluene induces distal RTA was that these patients did not lower their urine pH below 5.5

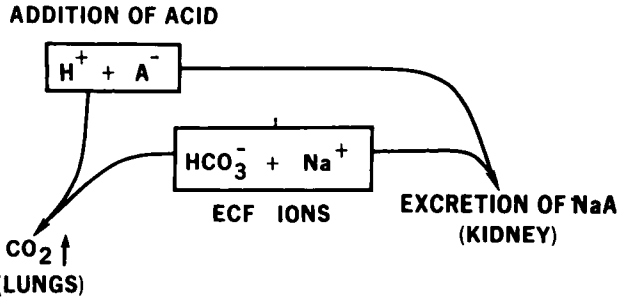

Figure 3. "Indirect" loss of sodium bicarbonate. Na and bicarbonate are present in the body (larger rectangle). There are two components to the loss of Na and bicarbonate: (*1*) there is production of an acid (H^+) other than carbonic acid (smaller rectangle); and (*2*) the anion or conjugate base of that acid (A^-) is excreted in the urine with Na or K and not H^+ or NH_4^+. Thus, there is loss of $NaHCO_3$ from the body. (From reference 43, with permission).

during metabolic acidosis. How important is the urine pH in the diagnosis of distal RTA? As discussed above, distal RTA represents a group of disorders that are characterized by a reduction of renal new bicarbonate generation. Because the major component of this new bicarbonate generation is a function of glutamine metabolism in the proximal tubule cells, with addition of bicarbonate to the ECF and NH_4^+ to the urine, distal RTA can then be simply defined as a low NH_4^+ excretion disease (24,26). Thus, the important question is, "is the urine pH a reliable indicator of renal new HCO_3 generation in a patient with metabolic acidosis?"

The focus of distal RTA changed from a disease of low excretion of NH_4^+ (24) to one where the urine pH became paramount. The reason for this change in emphasis is not clear to us. The urine pH was used as an indirect indicator of the rate of excretion of NH_4^+ and titratable acid (30). With respect to the latter, a fall in pH from 6 to 5 has only a minor impact on the rate of excretion of H^+ as titratable acid, as there are few buffers in the urine in this pK range. With respect to the excretion of NH_4^+, the evidence summarized in Figure 2 (31) is even more compelling. A urine pH of 6 signals a low rate of excretion of NH_4^+ in acute metabolic acidosis, but a high rate of excretion of NH_4^+ in chronic metabolic acidosis. What, then, does a urine pH of 6 mean in a patient who abuses toluene? Because the clinician cannot answer that question with confidence, an estimate of the rate of excretion of NH_4^+ must be obtained in some other way.

The concentration of NH_4^+ in the urine may be measured directly, or an indirect estimate may be obtained by using the urine osmolal gap (14), as in the discussion of the index case. Calculation of the urine net charge does not reflect the rate of excretion of NH_4^+ when large amounts of unmeasured anions (hippurate) are present in the urine (32). Although the usual rate of excretion of NH_4^+ is 30 to 40 mmol/day, when faced with chronic metabolic acidosis, normal individuals can excrete 200 to 300 mmol/day (33,34). There is a lag period, however, of a few days before an appreciable increase in the rate of excretion of NH_4^+ can be achieved; hence, it is important to know the duration of acidosis to make a quantitative assessment of the appropriateness of this renal response.

Of the eight patients who abused toluene and were studied during metabolic acidosis, only two had a very low rate of excretion of NH_4^+, and, hence, distal RTA (Table 3). Six did not have such a low rate of excretion of NH_4^+. Without knowing the duration of acidosis, one cannot make an unequivocal statement about the appropriateness of the renal response; one can, however, safely say that in this latter group of patients, the kidney was not the "sole" cause of acidosis. It follows that the high rate of production of acid was a critical component of the pathogenesis of metabolic acidosis in these patients.

The rate of excretion of NH_4^+ was very high (>595 μmol/min) in one of the patients reported in Table 3. In fact, this rate of excretion is more than twofold higher than that observed in normal subjects given a chronic acid load (33,34). There are two ways to interpret this observation. On the one hand, one could question the reliability of the observation and perhaps speculate that there was production of NH_4^+ in the urine after it was formed (a urea-splitting organism). Alternatively, it is possible that there was indeed an unusually high production of NH_4^+ in this setting. One hypothesis, among others, is that there was activation of the gamma-glutamyl transferase pathway of production of NH_4^+ by hippurate (35). Notwithstanding, we doubt that enough substrate would be available for this enzyme to account for this unusual observation. Hence, we would favor the former explanation.

If these high rates of excretion of NH_4^+ are an important response by the kidney to the organic acid load resulting from the metabolism of toluene, subjects who regularly abuse toluene for long periods may have chronically elevated rates of excretion of NH_4^+. Increased concentrations of NH_3 in the interstitium have been reported to lead to medullary-interstitial disease by complement activation (36). Thus, toluene abuse might ultimately cause chronic interstitial disease, impairing the transfer of NH_4^+ into the urine, and eventually causing distal RTA and low rate of excretion of NH_4^+.

3. The Urine PCO_2

The inability to increase the PCO_2 in a highly alkaline urine to an appropriate degree is considered as evidence for impaired proton secretion in the distal nephron (37). More recently, DuBose and Caflisch (38) have provided further supportive evidence for the validity of that test in a variety of experimental models of distal RTA.

The only data available in the literature on urine PCO_2 in toluene sniffers are those provided by Batlle *et al.* (10) on three patients. The urine PCO_2 was lower in the patients than in normal subjects with a comparable concentration of bicarbonate in the urine. The highest PCO_2 obtained in alkaline urine in patients was less than 60 mm Hg (mean 47 ± 8.8 mm Hg). Of note, however, in two of these three patients, the rate of excretion of NH_4^+ was 14 and 17 μmol/min, consistent with the diagnosis of distal RTA. Hence, these data reflect events in a subset of the population which is expected to have a low PCO_2 of the urine. To clarify this issue, observations are needed in toluene abuse and patients with higher

rates of excretion of NH_4^+. Even in those patients who have low secretion of H^+, a causal relationship between toluene sniffing and a low rate of excretion of NH_4^+ has not been established.

4. Studies with the Urinary Bladder of the Turtle

Batlle *et al.* (10) demonstrated that acidification was decreased by toluene in the turtle bladder *in vitro*. It did not impair the transport of Na, and the defect was not that of back-leak because toluene did not impair the proton motive force (mucosal pH at which J_H^+, the secretion of H^+, was zero). Notwithstanding, the dose of toluene that was demonstrated to suppress secretion of H^+ was 10- to 100-fold higher than the highest level of toluene observed in the blood in their patients. H^+ secretion was unchanged when the turtle bladder was exposed to levels similar to those seen in patients. Unless higher levels of toluene are present in the distal nephron, this *in vitro* experimental evidence that toluene impairs distal acidification cannot be interpreted as conclusive proof that toluene is the agent responsible for the low concentration of H^+ in the urine.

ELECTROLYTE DISTURBANCES AFTER TOLUENE ABUSE

In addition to the acid-base aberrations, fluid and electrolyte abnormalities are very important in the clinical analysis. In fact, nausea and generalized weakness which may result from the ECF volume contraction and hypokalemia are symptoms that often prompt the patient to seek medical attention.

Hippurate is excreted rapidly not only because of the filtration but also because of the tubular secretion of this anion; its renal clearance approximates renal plasma flow. The excretion of hippurate mandates the excretion of a cation which may be NH_4^+, Na, or K. Because the excretion of NH_4^+ is initially limited, losses of Na or K can be substantial. Bennett *et al.* (39) observed that after the infusion of *p*-aminohippurate in humans, the rate of excretion of Na in the urine increased sixfold. Increased loss of K in the urine has also been observed after the experimental infusion of *p*-aminohippurate (39,40).

About one in four of the patients who present with toluene abuse has very severe hypokalemia (<2 mmol/liter) (Figure 4). There are a number of factors which might influence the distribution of K between the ECF and the ICF in this setting. The degree of hypokalemia may underestimate the degree of depletion of K because of a shift of K into the ECF, which may be the result of the metabolic acidosis, low levels of insulin due to high levels of alpha adrenergics secondary to hypovolemia, and the possibility of rhabdomyolysis secondary to hypokalemia and hypophosphatemia (41). In addition, there are factors which could contribute to the kaliuresis. First, one might anticipate that there will be increased levels of mineralocorticoid owing to ECF volume contraction. Secondly, augmented kaliuresis is produced if the urine contains poorly reabsorbed anions *plus* a concentration of Cl in the urine which is <10 mmol/L (42). Both of these criteria could be met as ECF volume contraction would be associated with very little Cl in the urine and hippurate or benzoate would be the anions which accompanied the Na and K in the urine. Lastly, the rate of flow of urine might be high because of the osmotic load of hippurate and its associated cations. These factors in combination give rise to the profound K loss and hypokalemia seen in these patients.

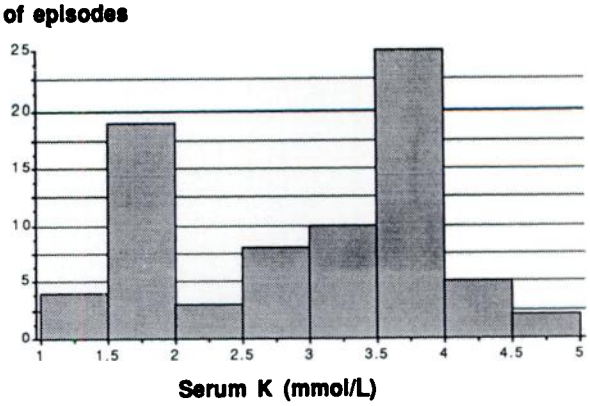

Figure 4. The concentration of K in the serum of patients with toluene abuse. The number of presentations of toluene abuse (total, 77) is plotted against the concentration of potassium in the serum. The majority of patients suffered from hypokalemia at presentation.

CONCLUSIONS

There is a spectrum of disorders that are responsible for the metabolic acidosis associated with toluene abuse (Table 5). On the one hand, there is clearly overproduction of hippuric acid. On the other hand, only some of the patients (two of eight) have an overt reduction of excretion of net acid (NH_4^+). The question remains open, "is the renal defect, when present, a direct result of toxicity of toluene or one of its metabolites?"

More data are required, and patients with toluene abuse should be studied early after presentation. The following investigations should be obtained. The most important test is to measure, directly, the concentration of NH_4^+ in the urine; as we have seen, calculation of the urine net charge will not provide a reliable indication of the concentration of NH_4^+ in the urine due to the increased rate of excretion of organic anions. Calculation of the osmolal gap in the

TABLE 5. Pathophysiology of the metabolic acidosis in toluene abuse

1. High rate of production of organic acids (hippuric and benzoic acids) in the presence of normal renal function.
   - Usually hyperchloremic acidosis
   - Wide anion gap if production exceeds excretion of these anions
2. High rate of production of organic acids with the presence of a degree of impairment in the rate of excretion of NH_4^+.
   - Production of hippuric and benzoic acids as above.
   - Low rate of excretion of NH_4^+.
     - Reduced production of NH_4^+ in the renal cortex (usually a low GFR)
     - Low transfer of NH_4^+ to the urine (low secretion of H^+ in distal nephron)
       - related to a direct effect of toluene?
       - medullary damage that is an indirect effect of toluene or unrelated to this agent
3. Other causes of metabolic acidosis unrelated to toluene

urine may be of value; for this, the urine osmolality, Na, K, urea, and glucose are required. Follow-up studies where the urine PCO_2 is measured in patients with high or low rates of excretion of NH_4^+ will also help define the type and extent of the renal lesion affecting the excretion of net acid. Finally, the concentrations of hippuric and benzoic acids in blood and urine can help quantitate the contribution of overproduction of organic acids over the clinical course in patients who had inhaled toluene.

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REFERENCES

1. **Taher S, Anderson R, McCartney R, Popovtzer M, Schrier R:** Renal tubular acidosis associated with toluene "sniffing." N Engl J Med 1974; 290:765–768.
2. **Steinmetz P, Al-Awqati Q, Lawton W:** Specialty rounds: Nephrology rounds, University of Iowa Hospitals: Renal tubular acidosis. Am J Med Sci 1976;271:40–54.
3. **Fischman C, Oster J:** Toxic effects of toluene: A new cause of high anion gap metabolic acidosis. JAMA 1979;241:1713–1715.
4. **Bennett R, Forman H:** Hypokalemic periodic paralysis in chronic toluene exposure. Arch Neurol 1980;37:673.
5. **Moss A, Gabow P, Kaehny W, Goodman S, Haut L:** Fanconi's syndrome and distal renal tubular acidosis after glue sniffing. Ann Intern Med 1980;92:69–70.
6. **Streicher H, Gabow P, Moss A, Kono D, Kaehny W:** Syndromes of toluene sniffing in adults. Ann Intern Med 1981;94:758–762.
7. **Voigts A, Kaufman C Jr:** Acidosis and other metabolic abnormalities associated with paint sniffing. South Med J 1983;76:443–447.
8. **Patel R, Benjamin J Jr:** Renal disease associated with toluene inhalation. Clin Toxicology 1986;24:213–223.
9. **Lavoi F, Dolan M, Danzl D, Barber R:** Recurrent resuscitation and 'no code' orders in a 27-year-old spray paint abuser. Ann Emerg Med 1987;16:1266–1273.
10. **Batlle D, Sabatini S, Kurtzman N:** On the mechanism of toluene-induced renal tubular acidosis. Nephron 1988;49:210–218.
11. **Goodwin T:** Toluene abuse and renal tubular acidosis in pregnancy. Obstet Gynecol 1988;71: 715–718.
12. **Martinez J, Sala J, Vea A, Casals E:** Renal tubular acidosis with an elevated anion gap in a 'glue-sniffer.' Hum Toxicol 1989;8:139–140.
13. **Ethier J, Kamel K, Magner P, Lemann JJ, Halperin M:** The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. Am J Kidney Dis 1990;15:309–315.
14. **Halperin ML, Margolis BL, Robinson LA, Halperin RM, West ML, Bear RA:** The urine osmolal gap: A clue to estimate urine ammonium in 'hybrid' types of metabolic acidosis. Clin Invest Med 1988;11:198–202.
15. **Russ G, Clarkson A, Woodruff A, Seymour A, Cheng I:** Renal failure from "glue sniffing." Med J Aust 1981;2:121–122.
16. **Taverner D, Harrison D, Bell G:** Acute renal failure due to interstitial nephritis induced by 'glue-sniffing' with subsequent recovery. Scott Med J 1988;33:246–247.
17. **Benignus V:** Health effects of toluene: A review. Neurotoxicology 1981;2:567–588.
18. **Blake RI, Coon M:** On the mechanism of action of cytochrome P-450. Role of peroxy spectral intermediates in substrate hydroxylation. J Biol Chem 1981;256:5755–5763.
19. **Blake RI, Coon M:** On the mechanism of action of cytochrome P-450. Evaluation of homolytic and heterolytic mechanisms of oxygen-oxygen bond cleavage during substrate hydroxylation by peroxides. J Biol Chem 1981;256:12127–12133.
20. **Von Oettingen W, Neal P, Donahue D:** The toxicity and potential dangers of toluene. JAMA 1942;118:579–584.
21. **Swan RC, Pitts RF:** Neutralization of infused acid by nephrectomized dogs. J Clin Invest 1955;34:205–212.
22. **Smith H, Finkelstein N, Aliminosa L, Crawford B, Graber M:** The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dogs and man. J Clin Invest 1945; 24:388–404.
23. **Press E, Done A:** Solvent sniffing. Physiological effects and community control measures for intoxication from the intentional inhalation of organic solvents. Pediatrics 1967;39:451–461.
24. **Albright F, Burnett C, Parson W, Reifenstein EJ, Roos A:** Osteomalacia and late rickets: Various etiologies met in United States with emphasis on that resulting from specific form of renal acidosis, therapeutic indications for each etiological subgroup, and relationship between osteomalacia and Milkman's syndrome. Medicine

1946;25:399–479.
25. **Bank N, Schwartz WB:** Influence of certain urinary solutes on acidic dissociation constant of ammonium at 37°C. J Appl Physiol 1960; 15:125–127.
26. **Carlisle E, Donnelly S, Halperin M:** Recognize the ammonium defect and pHorget the urine pH. Pediatr Nephrol 1991, in press.
27. **Emmett M, Narins R:** Clinical use of the anion gap. Medicine 1977;56:38–54.
28. **Oh M, Carroll H:** The anion gap. N Engl J Med 1979;297:814–817.
29. **Gabow P, Kaehny W, Fennessey D, Goodman S, Gross P, Shrier R:** Diagnostic importance of an increased anion gap. N Engl J Med 1980;303:854–858.
30. **Wrong O, Davies W:** The excretion of acid in renal disease. Q J Med 1959;23:259–313.
31. **Richardson RMA, Halperin ML:** The urine pH: A potentially misleading diagnostic test in patients with hyperchloremic metabolic acidosis. Am J Kidney Dis 1987;10:140–143.
32. **Goldstein M, Bear R, Richardson R, Marsden P, Halperin M:** The urine anion gap: A clinically useful index of ammonium excretion. Am J Med Sci 1986;292:198–202.
33. **Madison LL, Seldin DW:** Ammonia excretion and renal enzymatic adaptation in human subjects, as disclosed by administration of precursor amino acids. J Clin Invest 1958;37:1615–1627.
34. **Simpson D:** Control of hydrogen ion homeostasis and renal acidosis. Medicine 1971;50:503–541.
35. **Welbourne T, Dass P:** Gamma glutamyltransferase contribution to renal ammoniagenesis in vivo. Pflugers Arch 1988;411:573–578.
36. **Nath K, Hostetter M, Hostetter T:** Pathophysiology of chronic tubulo-interstitial disease in rats. J Clin Invest 1985;76:667–675.
37. **Halperin M, Goldstein M, Haig A, Johnson M, Stinebaugh B:** Studies on the pathogenesis of type I (distal) renal tubular acidosis as revealed by the urinary PCO_2 tensions. J Clin Invest 1974;53:669–677.
38. **DuBose TJ, Caflisch C:** Validation of the difference in urine and blood carbon dioxide tension during bicarbonate loading as an index of distal nephron acidification in experimental models of distal renal tubular acidosis. J Clin Invest 1985;75:1116–1123.
39. **Bennett W, Roberts D, Porter G:** The natriuretic effect of p-aminohippurate in man. Nephron 1976;16:197–204.
40. **Selkurt E, Shade J:** Effect of p-aminohippurate on renal excretion of potassium by the monkey kidney. Am J Physiol 1969;217:951–954.
41. **Mizutani T, Oohashi N, Naito H:** Myoglobinemia and renal failure in toluene poisoning: A case report. Vet Hum Toxicol 1989;31:448–450.
42. **Carlisle E, Donnelly S, Quaggin S, *et al.*:** Studies on the effects of anion excretion on potassium secretion in man. Clin Res 1990;38:537A.
43. **Halperin M, Goldstein M:** Fluid, Electrolyte and Acid-Base Emergencies. Philadelphia: WB Saunders & Co; 1987.