Urinary alkoxyacetic acids and renal effects of exposure to ethylene glycol ethers

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Abstract

Objectives—Ethylene glycol ethers and their acetates are widely used in industry, because of their hydrophilic and simultaneously lipophilic properties. Ethylene glycol ethers and their acetates are mainly metabolised to alkoxyacetic acids, but there is also a minor pathway through ethylene glycol to oxalic acid. The main pathway of ethylene glycol ethers is associated with significant clinical or experimental health effects and the minor pathway is also interesting because formation of urinary stones depends principally upon the urinary concentration of oxalate and calcium.

Methods—Excretion of alkoxyacetic and oxalic acids was examined among silkscreen printers for an entire working week. The aim of the study was to evaluate alkoxyacetic acids as early indicators of exposure to glycol ethers and to evaluate their toxicity to kidneys. The load of alkoxyacetic and oxalic acids was compared with the excretion of calcium, chloride, ammonia, and glycosaminoglycans (GAG). Morning urine was chosen for the main analysis, as the overall metabolite, ethoxyacetic acid (EAA), has a long elimination time from the body.

Results—The excretion of calcium increased according to the urinary alkoxyacetic acid load. The excretion of ammonia and chloride was higher among

the exposed workers than among the controls. The highest urinary alkoxyacetic acid load was also associated with increased excretion of GAG, which may reflect the toxicity of metabolites of ethylene glycol ether. The excretion of GAG correlated positively with that of calcium in the printers with highest exposure. The tendency to form urinary stones was 2.4-fold higher among silkscreen printers than among office workers.

Conclusion—On the basis of renal effects our study indicates the need for establishing a new biological exposure limit before a workshift that is clearly below 100 mmol ethoxyacetic acids per mol creatinine in morning urine of people occupationally exposed to ethylene glycol ethers.

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Figure 1 Metabolic pathway of alkoxyethanol acetate.^{2,4}

Ethylene glycol ethers and their acetates are widely used in industry, because of their hydrophilic and simultaneously lipophilic properties. Glycol ethers do not have special warning properties—for example, odour—and they rapidly enter the body unnoticed. Glycol ethers have low vapour pressure, but they are readily absorbed through the skin.¹

Ethylene glycol ethers and their acetates are mainly (60%-80%) metabolised through alkoxyacetaldehydes to alkoxyacetic acids (fig 1). There is also a minor (10%-15%) pathway (fig 1) through ethylene glycol, glycolaldehyde, glycolic acid, and glyoxylic acid to oxalic acid.²⁻⁴

The main pathway of ethylene glycol ethers through acetaldehyde to alkoxyacetic acids is associated with significant clinical or experimental health effects. Exposure to ethylene glycol ethers is associated with haematological problems,^{5,6} oligospermia, azoospermia,⁷ and reproductive problems.⁸ Animal studies indicate that they can induce germ cell toxicity, reproductive toxicity, and teratogenicity, and some of them are potential carcinogens.⁹

The minor pathway is also interesting because formation of urinary stones depends principally upon the urinary concentration of oxalate and calcium, although the percentage of oxalate in stones is higher than that of calcium.¹⁰ On the other hand, calcium oxalate nephrolithiasis is associated with a defect in erythrocyte oxalate self exchange and an

abnormal rate of phosphorylation of erythrocyte membrane protein.¹¹ The glycosaminoglycan (GAG) content of erythrocyte ghosts is found to be lower than normal in patients who form stones. The GAG content correlates inversely with oxalate self exchange and band 3 phosphorylation in erythrocytes. The erythrocyte oxalate is transported by way of band 3 protein, which shares the same functional similarities with anion exchangers, but it is not known whether non-erythroid anion exchangers are structurally related to it.¹² Anyway, the role of glycosaminoglycans as inhibitors of calcium oxalate crystallisation is controversial, and reported actions range from negligible¹³ and inhibitory¹⁴ to promoting.¹⁵

Karniski and Aronson have suggested that there are at least two separate anion exchangers mediating Cl⁻ transport on the luminal membrane of the rabbit proximal tubule cell. These exchangers may play important parts in mediating transtubular Cl⁻ and oxalate transport in this nephron segment.^{16,17} The proximal tubular cells also liberate ammonia from glutamine and the glutamate pool. It is possible that a higher oxalate concentration in these cells could also cause changes in the liberation of NH₄⁺ in humans.¹⁸

According to these findings, the excretion of large amounts of organic acids poses problems to renal tubular function, and the interference seems to change the function of the chloride exchanger in the kidney.¹⁹⁻²¹

From a clinical point of view in occupational health care, the kidney effects are probably the most interesting as most of the glycol ether metabolites are excreted in the urine. Therefore, additional knowledge on the possibility of a link between exposure to ethylene glycol ether and changes in renal functions would be advantageous. More information on the minor pathway of metabolism would also be important, because small changes in oxalate excretion have a greater impact on the saturation of calcium oxalate in urine than changes in calcium excretion.^{22,23} The changes in the excretion of proteoglycans may be secondary, but they may reflect more chronic changes in the kidney. All variables are valuable with a view to validating the current biological exposure indices for ethylene glycol ethers and their congeners.

Methods

Eight silkscreen printers from four worksites participated in this study on a voluntary basis. Their ages varied from 20 to 40 years and they

were all considered to be healthy. Urine samples were collected before and after the workshift in 56 instances and analysed for alkoxyacetic and oxalic acids, ammonia, calcium, and pH. Urinary analysis before a workshift was completed with assay of GAGs and chloride (table 1). Twenty one office workers who were not exposed to ethylene glycol ethers were the control group. They were considered healthy and they gave urine samples before their workshift. Samples were not included in the study if the concentration of creatinine was below 2 mmol/l.

All of the collected urine samples were kept at -20°C before the analysis, and those obtained for the oxalic acid analysis were not stored with preservatives. Methoxyacetic acid (MAA), ethoxyacetic acid (EAA), butoxyacetic acid (BAA), and oxalic acid were analysed with the modified gas chromatographic method described by Sakai *et al.*²⁴ The coefficients of variation within assays (n = 5) for MAA, EAA, BAA, and OA were 9.2%, 2.6%, 1.4%, and 3.4%, respectively, at a concentration of 20 mg/l. Calcium was analysed with a spectrophotometer,²⁵ ammonia with a reflectometer²⁶ and GAGs by the method of Savolainen.²⁷

The workers were divided into four groups according to the alkoxyacetic acid burden. The purpose of the study was to evaluate the dose-response relation between the exposure and excretion. The first group (> 100 mmol alkoxyacetic acid/mol creatinine) and second group (100–50 mmol/mol creatinine) were formed with two international limit values for EAA, 110 mmol/mol creatinine (American Conference of Governmental Industrial Hygienists (ACGIH) 1994–5),²⁸ and 55 mmol/mol creatinine (Deutsche Forschungsgemeinschaft (DFG) 1994).²⁹ Limits for the third and fourth groups were chosen to be 50–20 mmol/mol and 20–0 mmol alkoxyacetic acid per mol creatinine. The limit value for EAA was chosen, because the portion of MAA, EAA, and BAA of total excretion of alkoxyacetic acids were on average 1.0%, 93.6%, and 5.4%, respectively.

The significance of the difference in the excretion of oxalic acid, calcium, ammonia, chloride, pH, and GAG between the exposed and unexposed groups was tested by analysis of variance (ANOVA). The results for the exposed group were repeated observations from the same set of people and for the unexposed group they were single values. The statistical differences between exposed and control groups of the excretions and excretion pattern were tested separately each day. The

Table 1 Mean (SEM) excretions of silkscreen printers after the shift compared with those of controls

	Controls	Silkscreen printers						
		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
AAA (mmol/mol creatinine)	ND	44 (18)	71 (30)	77 (22)	87 (27)	94 (35)	59 (23)	46 (17)
Oxalic acid (mmol/mol creatinine)	38 (3)	49 (11)	43 (5)	36 (4)	53 (8)†	54 (15)	55 (12)†	47 (6)
Calcium (mmol/mol creatinine)	243 (30)	211 (37)	217 (43)	176 (39)	193 (22)	261 (62)	320 (69)	233 (47)
Ammonia (mmol/mol creatinine)	2.8 (0.6)	3.6 (0.5)	3.2 (0.5)	4.0 (0.7)	4.0 (0.5)	3.7 (0.3)	4.0 (0.3)	3.3 (0.3)
pH	6.4 (0.3)	6.0 (0.3)	6.3 (0.2)	5.8 (0.2)	5.8 (0.2)†	6.1 (0.2)	5.7 (0.2)†	5.9 (0.2)
P value (mva)	—	0.2505	0.9389	0.0864†	0.0357*	0.2787	0.0899*	0.1912

*P < 0.05; †P < 0.1.

ND = not detected; AAA = alkoxyacetic acids; mva = multivariate analysis.

Table 2 Mean (SEM) excretions of silkscreen printers before shifts compared with those of controls

	Controls	Silkscreen printers						
		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
AAA (mmol/mol creatinine)	ND	30 (15)	27 (9)	70 (31)	88 (39)	82 (26)	87 (36)	45 (20)
Oxalic acid (mmol/mol creatinine)	38 (3)	36 (3)	32 (4)	42 (4)	42 (4)	41 (6)	34 (3)	35 (7)
Calcium (mmol/mol creatinine)	243 (30)	437 (87)*	332 (73)	373 (77)†	452 (105)*	337 (51)	291 (30)	166 (35)
Ammonia (mol/mol creatinine)	2.8 (0.6)	4.0 (0.5)†	4.7 (0.8)†	4.7 (0.8)†	4.9 (0.5)*	4.4 (0.6)†	3.5 (0.3)	3.8 (0.3)
pH	6.4 (0.3)	5.9 (0.2)	5.7 (0.1)†	6.0 (0.2)	6.0 (0.2)	5.7 (0.2)	5.7 (0.2)†	5.5 (0.1)*
P value (mva)	—	0.2312	0.1993	0.3135	0.0699†	0.1916	0.4658	0.0129*
GAG (g/mol creatinine)	4.7 (0.5)	4.4 (1.1)	4.5 (1.0)	4.3 (0.7)	7.0 (1.5)	4.5 (0.8)	4.8 (1.4)	2.9 (0.8)†
Chloride (mol/mol creatinine)	10.9 (1.3)	17.3 (4.1)†	13.8 (1.6)	13.3 (2.2)	19.3 (6.5)	16.7 (3.2)†	20.0 (6)	9.2 (1.7)

*P < 0.05; †P < 0.1.

ND = not detected; GAG = glycosaminoglycans; AAA = alkoxyacetic acids; mva = multivariate analysis.

significance of the difference in the excretion patterns between exposed and control groups were tested with multivariate analysis, which included oxalic acid, calcium, ammonia, and pH, because they had same control group.

The tendency (T) for subjects to form stones was estimated by calculating the shortest distance (D) of calcium ($= x_1$) and oxalic acid ($= y_1$) values from the supersaturation curve $\{x, (3655907.93a^{-0.97})(x^{-0.97})\}$ by a computer program (Mable V, Waterloo Mable Software, Waterloo, Ontario, Canada) for symbolic mathematics. For each subject a saturation curve was corrected according to the excretion of creatinine (a). Distances were

marked negative for subjects who exceeded the saturation point ($x_1 > x$). The T was calculated by the equation $T = 1/D(\text{mean})$.³⁰

Results

The results were separated into urine analyses before and after the shift. The analysis after the shift did not show any dose-response relation between the alkoxyacetic acid burden and the excretion of calcium, ammonium, or the pH. The urinary excretion of alkoxyacetic acids increased during the working week and the highest levels of excretion occurred on Friday evening. The highest peak of oxalic acid was

Figure 2 Relation between the excretion of alkoxyacetic acids and that of calcium, GAG, ammonia and chloride. The results are given as the means (SEM).

Figure 3 Relation between the excretion of GAG and calcium in the most exposed group ($y = 120.74x + 48.34$, $r = 0.75$).

also found at the end of the week. The excretion of oxalic acid and pH differed moderately from controls on Thursday and Saturday. The excretion patterns of exposed workers differed moderately from those of the control group on Wednesday and Saturday and significantly on Thursday evening (table 1).

Urinary ammonia, calcium, or pH before the shift differed significantly from those of controls

on Monday, Thursday, and Sunday mornings (table 2), and the excretion of calcium seemed to follow the alkoxyacetic acid burden (fig 2). The excretion of chloride was higher among the exposed workers than among the controls (fig 2). The excretion patterns of exposed workers differed moderately from those of controls on Thursday and significantly on Sunday morning (table 2).

The mean excretion of GAG seemed to decrease from the control group to the second most highly exposed group but the mean excretion in the most highly exposed group was by far the greatest (fig 2). The excretion of glycosaminoglycans (y) correlated positively ($y = 120.74x + 48.34$, $r = 0.75$) with that of calcium (x) in this group (fig 3).

The calculated distance (mean (SEM)) from the supersaturation curve were among unexposed workers, silkscreen printers before the shift, and silkscreen printer after the shift (149 (20), 62 (9), and 104 (18) respectively). The mean tendencies to form urinary stones were 0.006, 0.016, and 0.010, respectively.

Figure 4 (A) Unmodified supersaturation curve for calcium oxalate,³¹ (B) modified supersaturation curve for control samples according to the mean excretion of creatinine (11.13 mmol/l), (C) modified curve for samples from silkscreen printers before a workshift according to the mean excretion of creatinine (14.20 mmol/l), and (D) modified curve for samples from silkscreen printers after a workshift according to the mean excretion of creatinine (12.55 mmol/l). All cases in the different groups have been plotted into the figures and results of silkscreen printers are comparable with the same scaled results of the controls.

Discussion

The urinary analysis after the shift did not show any significant differences between the exposed and unexposed workers (table 1). This lack of correlation may have been caused by the long biological half life of the metabolites in the main metabolic pathway. The half life of alkoxyacetic acids decreases as the length of the alkyl chain increases. The half lives for MAA, EAA, and BAA are 71, 42, and six hours, respectively.^{2,31-33} This could also cause a metabolic adaptation to the generation of the organic acid metabolites in kidneys. Most of MAA, EAA, and BAA is not typically conjugated with glycine.³ Therefore, a significant reabsorption probably occurs also in the tubular section of the nephron. The liberation of ethylene glycol represents the minor metabolic pathway of ethylene glycol ethers. The half life of ethylene glycol is about three to eight hours and the highest peak occurs in blood one to four hours after exposure.³⁴ Therefore, it seems that the end metabolite of ethylene glycol, oxalic acid, does not accumulate during a working week when the doses of ethylene glycol ethers are moderate.

A formate and chloride exchanger protein has been isolated from the kidney membrane fraction.³⁵ It may also accept anions other than formate or oxalate in the exchange system, as in our study the urinary chloride concentration followed that of acids (fig 2). The exchanger was inhibited by furosemide, and one wonders what effects its use would have on the kinetics of alkoxyacetic acids. In one case of intoxication, a dose of furosemide helped the victim to survive a very high dose of formic acid.³⁶

It is interesting to note that the urinary ammonia increased with increasing urinary alkoxyacetic acid (fig 2). It is possible that alkoxyacetic acids change the renal ammoniogenesis at high concentrations as does formic acid.²⁰ As ammonia occurs in the urine primarily as NH_4^+ ion, its excretion would require the excretion of an equivalent number of anions such as chloride or phosphate. This link was also found in our study (fig 2). Free ammonia is very toxic and it cannot be transported through the blood; therefore it is converted into an amide group of glutamine by glutamine synthetase.

The highest urinary acid load is also associated with increased proteoglycan excretion, which may also reflect the toxicity of the glycol ether metabolites (fig 2). The excretion of GAG seems to decrease with the load of alkoxyacetic acids in moderate exposure as was found to be the case in our previous study among car mechanics.³⁷ Baggio *et al* also found a lower GAG content in erythrocyte ghosts in patients who form stones than in normal people.¹¹

Calciuria could also qualify as a renal effect indicator because of the associated risk of nephrolithiasis. It is interesting to note that the proteoglycan excretion peak coincided with the highest rate of calcium excretion. It has been maintained that urinary proteoglycans prevent the crystallisation of urinary calcium salts.³⁸ The excretion of calcium increased

with increasing alkoxyacetic acid. This occurrence in turn is positively correlated with that of GAG (fig 3). The increase in urinary GAG may explain the finding that none of our cases had a history of urinary stone disease despite the fact that the urinary calcium and oxalate concentrations were at or above the supersaturation line in many cases.

Formation of urinary stones starts rapidly when the products of the reaction of oxalic acid with calcium exceeds the supersaturation level. The tendency to form crystals in urine samples can be estimated roughly by hyperbolic function³⁰ (fig 4). Urine samples taken before the shift showed a higher tendency to form urinary stones than did samples taken after the shift. The calculated results indicated a 2.4-fold higher tendency for urinary stones among silkscreen printers than among office workers in samples taken before a shift (fig 4).

Dietary oxalate is thought to contribute 10% to 20% to urinary oxalate, 40% to 50% to endogenous metabolism, and the remaining 40% to 50% to the breakdown of ascorbic acid in the body.³⁹ It is well known that hormonal fluctuation may contribute more to the variability in oxalate excretion than for example the dietary intake of protein.⁴⁰ A good example of a hormonal effect is the fact that women excrete more oxalate relative to creatinine than men. The prevention of urolithiasis through a decreased dietary intake of calcium and oxalic acid is controversial because a decreased intake of calcium and oxalic acid increases the intestinal absorption and urinary concentration of calcium and oxalic acid.⁴¹ The role of exposure has been found to have a causal relation to urolithiasis among railway shopmen,⁴² and also in occupational groups with low physical activity. A similar relation has also been found with exposure to high temperatures and an increased fluid loss.⁴³

In conclusion, chronic occupational exposure to ethylene glycol ethers and their congeners is associated with important alkoxy and oxalic acids loads which alter renal function. The risk of urinary stones seems to be higher among silkscreen printers than among controls, and some of the changes are typical of chronic metabolic acidosis. It is very important to emphasise that ethylene glycol ethers are well absorbed through the skin and that analyses for their vapours mostly underestimate the exposure. Metabolites of ethylene glycol ethers also accumulate during the working week so that biological monitoring is the only means of obtaining an evaluation of total exposure. Our study also indicates the need, on the basis of renal effects, to establish a new biological exposure limit clearly below 100 mmol ethoxyacetic acids per mol creatinine, in the morning urine before a workshift, of people occupationally exposed to ethylene glycol ethers.

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