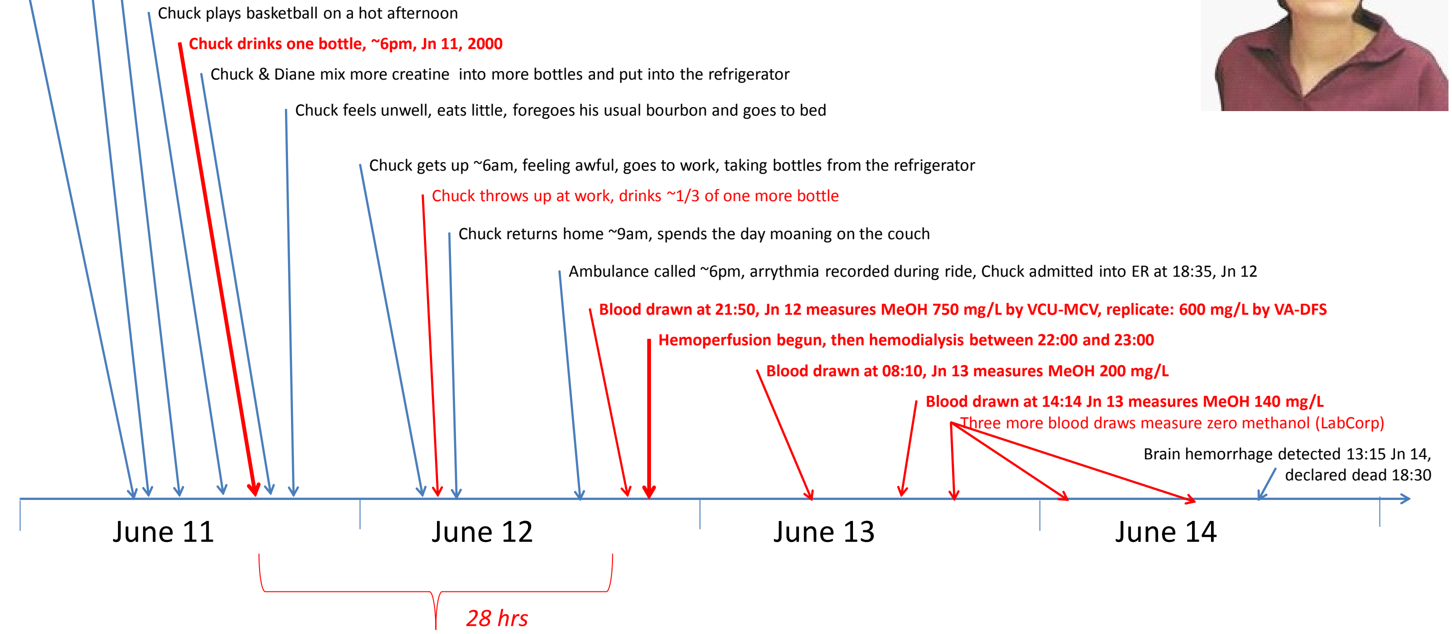
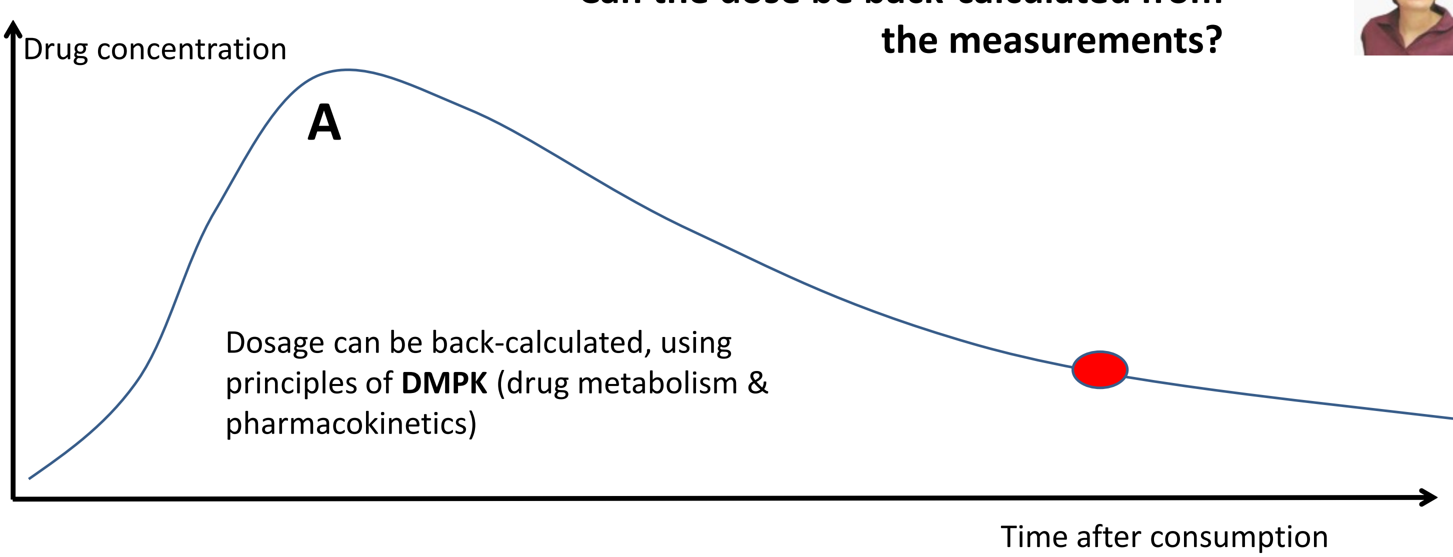
What are the facts of the timeline (according to plaintiff)?



Can the dose be back-calculated from the measurements?



What are the key facts to know about methanol in order to perform the back-calculation?

Methanol → **Formaldehyde** → **Formic acid**

A — **B** — **C**

MeOH Volume of Distribution: ~0.7 L/kg
Chuck Fleming body weight: 80kg

Alcohol dehydrogenase activity rate in alcoholics ~300 mg/L/hr ethanol
Alcohol dehydrogenase activity rate in alcoholics estimated at ~200 mg/L/hr methanol
zero-order kinetics for high doses

MeOH under hemodialysis half-life 2-3hrs, max
first-order kinetics

Is the half-life used in the calculation well-supported in the academic literature?

Kidney Int. 2015 Nov;88(5):1170-7. doi: 10.1038/ki.2015.232. Epub 2015 Aug 5.

Prediction and validation of hemodialysis duration in acute methanol poisoning.

Lachance P[1,2], Mac-Way F[1,2], Desmeules S[1,2], De Serres SA[1,2], Julien AS[3], Douville P[1,4], Ghannoum M[5], Agharazii M[1,2].

⊕ Author information

Abstract

The duration of hemodialysis (HD) in methanol poisoning (MP) is dependent on the methanol concentration, the operational parameters used during HD, and the presence and severity of metabolic acidosis. However, methanol assays are not easily available, potentially leading to undue extension or premature termination of treatment. Here we provide a prediction model for the duration of high-efficiency HD in MP. In a retrospective cohort study, we identified 71 episodes of MP in 55 individuals who were treated with alcohol dehydrogenase inhibition and HD. Four patients had residual visual abnormality at discharge and only one patient died. In 46 unique episodes of MP with high-efficiency HD the mean methanol elimination half-life (T1/2) during HD was 108 min in women, significantly different from the 129 min in men. In a training set of 28 patients with MP, using the 90th percentile of gender-specific elimination T1/2 (147 min in men and 141 min in women) and a target methanol concentration of 4 mmol/l allowed all cases to reach a safe methanol of under 6 mmol/l. The prediction model was confirmed in a validation set of 18 patients with MP. High-efficiency HD time in hours can be estimated using 3.390 × (Ln (MCi/4)) for women and 3.534 × (Ln (MCi/4)) for men, where MCi is the initial methanol concentration in mmol/l, provided that metabolic acidosis is corrected.

Chuck Fleming consumed up to four bourbons every night for >10years.

Where did the estimation for the rate of methanol elimination come from?

Forensic Sci Int. 1984 Jul;25(3):159-66.

The rate and kinetic order of ethanol elimination.

Winek CL, Murphy KL.

Abstract: The rate and kinetic order of ethanol elimination was evaluated in human volunteers. Part I of the study involved dosing individuals with alcoholic beverages on two separate occasions. Breathalyzer tests were performed at 15-min intervals for a period of 5 h. Attention was focused on values obtained after peak blood ethanol levels had been reached. The second part of the study included having samples drawn from alcoholics at predetermined intervals during recovery from alcoholic intoxication. Blood ethanol concentration data was analyzed for kinetic order and a comparison of ethanol elimination rates of alcoholics and non-alcoholics was made. The predicative capability of estimating a BAC from both the zero and first order theories was also investigated. It was concluded that ethanol elimination is a zero order process. For subjects classified as non-drinkers (consume less than 6 ounces of ethanol/month), the mean ethanol elimination rate as determined in the study was 12 +/- 4 mg/h. For subjects classified as social drinkers (consume more than 6 ounces but less than 30 ounces of ethanol/month), the mean ethanol elimination rate was 15 +/- 4 mg%/h, and for alcoholics, the mean ethanol elimination rate was 30 +/- 9 mg%/h. These results indicate that the rate of ethanol elimination increases with drinking experience.

(30 mg%/h = 30 mg/dL/hr = 300 mg/L/hr)

i.e. alcohol dehydrogenase is inducible. It has a higher activity in alcoholics

Clinical Investigation

Kidney International (2015) **88,** 1170–1177; doi:10.1038/ki.2015.232; published online 5 August 2015

Prediction and validation of hemodialysis duration in acute methanol poisoning

OPEN

Philippe Lachance[1,2], Fabrice Mac-Way[1,2], Simon Desmeules[1,2], Sacha A De Serres[1,2], Anne-Sophie Julien[3], Pierre Douville[1,4], Marc Ghannoum[5] and Mohsen Agharazii[1,2]

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DISCUSSION

Top

This study proposes a simple calculation derived from a kinetic model using the 90th percentile methanol elimination $T_{1/2}$ (147 min in men and 141 min in women) and targeting a methanol concentration of 4 mmol/l to predict the optimal duration of high-efficiency HD. This approach proved to be valid in our study cohort and achieved a safe methanol concentration in all cases. This study also suggests that our formula may obviate the need for costly monitoring of methanol concentrations during HD.

Methanol is a small molecule (32 Da), with a small volume of distribution (0.6–0.7 l/kg) and no protein binding. The elimination of methanol without an antidote is of zero order with an elimination rate of 85 mg/l/h at low concentration.[13] When fomepizole or ethanol is used, the apparent $T_{1/2}$ is significantly prolonged to ~54 and 43 h, respectively, with the total body elimination coming mostly from the lungs and the kidneys (<10 ml/min).[14, 15] The systematic review and the clinical guidelines published by the EXTRIP workgroup reported 114 patients, where the mean $T_{1/2}$ during HD was 3.4h (range: 0.6–13.1).[9] Recently, in 11 patients, Zacharof *et al.*[16] showed that the mean methanol elimination $T_{1/2}$ during HD was 3.7±1.4h. This is ~100min longer compared with the elimination $T_{1/2}$ reported in the present study. This difference is likely the result of lower blood flow, (180–250 ml/min vs. >350 ml/min), lower membrane surface area (1.5–1.6 m^2 vs. >2.0 m^2), and lower dialysate flow (500 ml/min vs. 750 ml/min) in their study. Whereas Hirsch's approach is mechanistically sophisticated, it is slightly complex and has only been validated in three cases of MP.[10, 12] Unfortunately, we could not validate Hirsch's approach in our cohort as the information on height was unavailable in clinical records, and therefore we could not estimate total body water using Watson's equation.

(85 mg/L/h + 10% for high concentration MeOH) * 2x induction of ADH = ~200 mg/L/h elimination rate of MeOH in Chuck Fleming, who consumed up to four bourbons every night for >10years.

Can you please recap again the key facts to know about methanol in order to perform the back-calculation?

Methanol → **Formaldehyde** → **Formic acid**

A **B** **C**

MeOH Volume of Distribution: ~0.7 L/kg
Chuck Fleming body weight: 80kg

Alcohol dehydrogenase activity rate in alcoholics ~300 mg/L/hr ethanol
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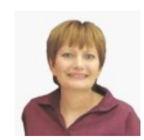
zero-order kinetics for high doses

MeOH under hemodialysis half-life 2-3hrs, max
first-order kinetics

Can you please show the math leading to the conclusion that the dosage is impossible?



MeOH blood measured, June 12 at 21:50 = 750 mg/L = 75mg/dL
MeOH Volume of Distribution: ~0.7 L/kg
Thus at blood sampling time = 0.7*750*80kg = **42** g MeOH remaining in Chuck Fleming's body.

>2x amount of "methanol" measured in each Gatorade bottle

Blood sampling time 21:50 Jun 12,
Consumption time ~18:00 Jun 11
= ~28 hrs between consumption and MeOH measurement

Alcohol dehydrogenase activity rate in alcoholics for methanol ~200 mg/L/hr
200*28hr = ~ 5.6g/L
5.6*0.7* 80kg = ~**310g** MeOH metabolized between consumption and blood measurement

Total theoretical dose = 42+310 **= 352g MeOH** Equivalent to >1L wiper fluid fitting inside 1.33 600mL bottles (=800mL).

(Absurd)

Conclusion: The analyte cannot be methanol

What methanol sources were shown on the Certificate of Analysis at trial in 2002?

Gatorade bottles (4): 3-4%   (3.3, 3.3. 3.6 and 4.3%)

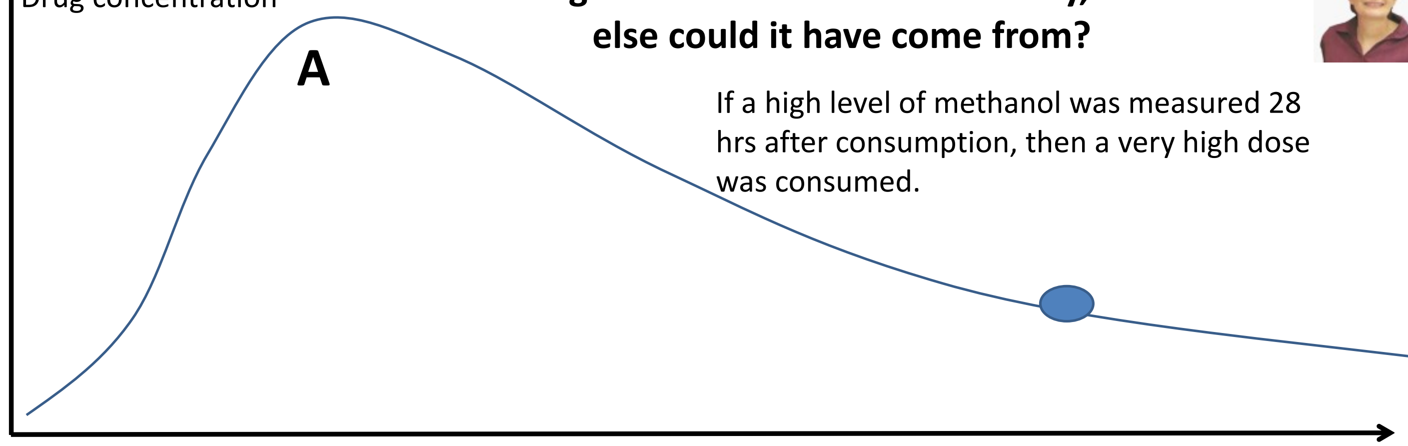
Wiper washer fluid: 30% methanol

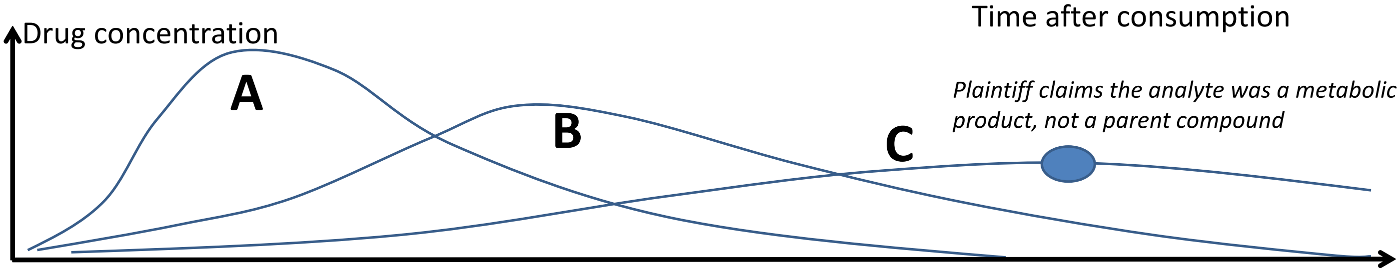
Why are these problematic sources of methanol?

- The amount of methanol in the consumed Gatorade bottles is too small by >10x. (3.3%*600mL *1.3 = <30g versus >300g calculated dose)
- The amounts of methanol measured in each bottle are too consistent to be from a liquid adulteration.
- The amount of fluid missing in the wiper fluid bottle is too small to account for the methanol in the Gatorade bottles.
- Washer fluid contains blue dye and Bitrex (world's most bitter substance)
- Neither blue dye nor Bitrex were confirmed in the Gatorade bottles.
- It would be impossible to drink a substance with Bitrex.
- No other sources of methanol found in the Fleming household.
- Unadulterated methanol cannot be purchased by ordinary people. Carol Gebert attempted to purchase pure methanol from Sigma-Aldrich and was denied.

If the dosage back-calculates to absurdity, then where else could it have come from?

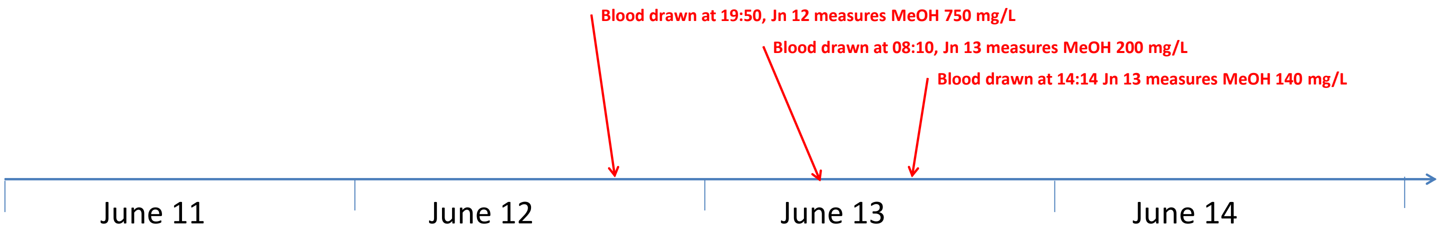
If a high level of methanol was measured 28 hrs after consumption, then a very high dose was consumed.





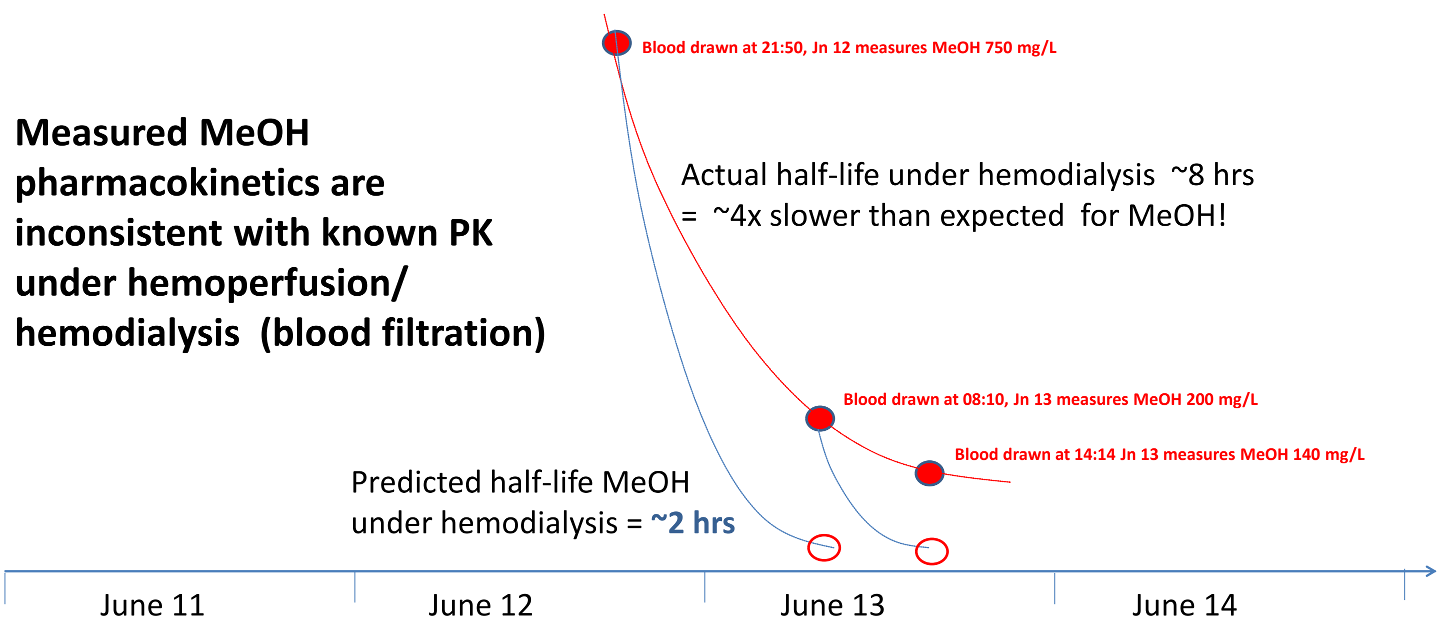
Are there other inconsistencies suggesting the analyte is not methanol?

MeOH under dialysis: first-order kinetics, half-life ~2hrs
1st blood sample 21:50, Jn 12 = 750 mg/L
Hemodialysis begins 22:00 Jn 12
(~10 hrs later equiv to ~4-5 MeOH half-lives)
Predicted 2nd sample conc ~20-50 mg/L
Actual 2nd blood sample 08:10, Jn 13 = 200 mg/L
(~6 hrs later equiv to 3 MeOH half-lives)
Predicted 3rd sample conc (based on 2nd) ~25 mg/L
Actual 3rd blood sample 14:14, Jn 13 = 140 mg/L

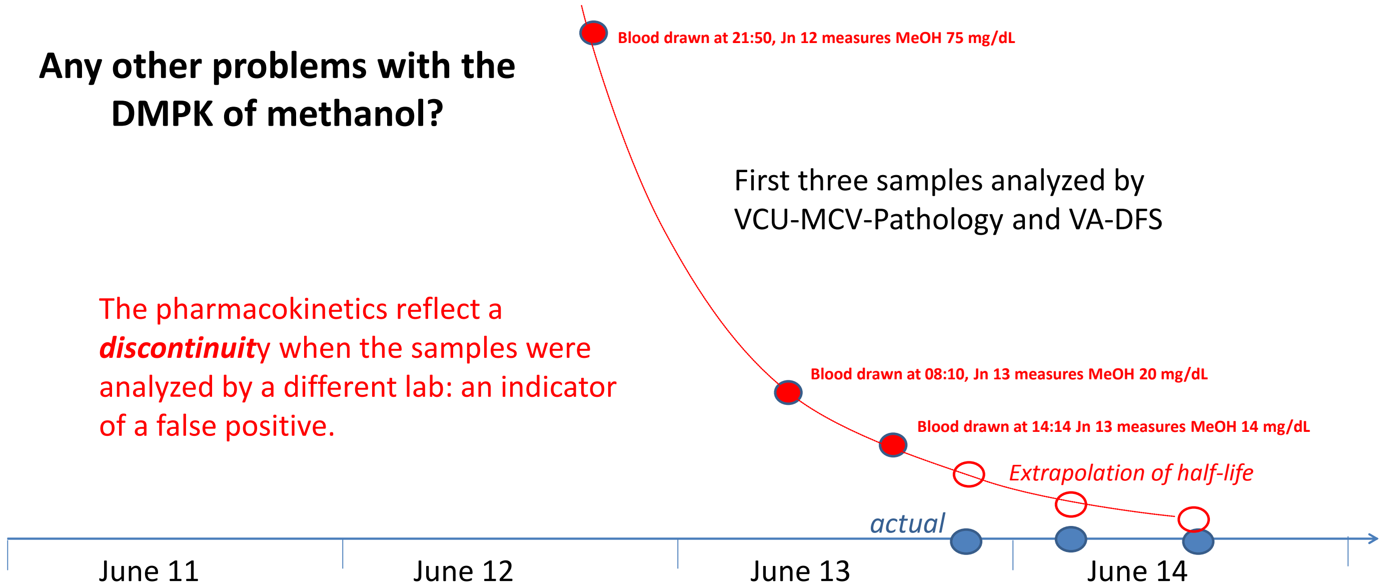


Can you show the court what that looks like graphically?

Measured MeOH pharmacokinetics are inconsistent with known PK under hemoperfusion/ hemodialysis (blood filtration)



Any other problems with the DMPK of methanol?

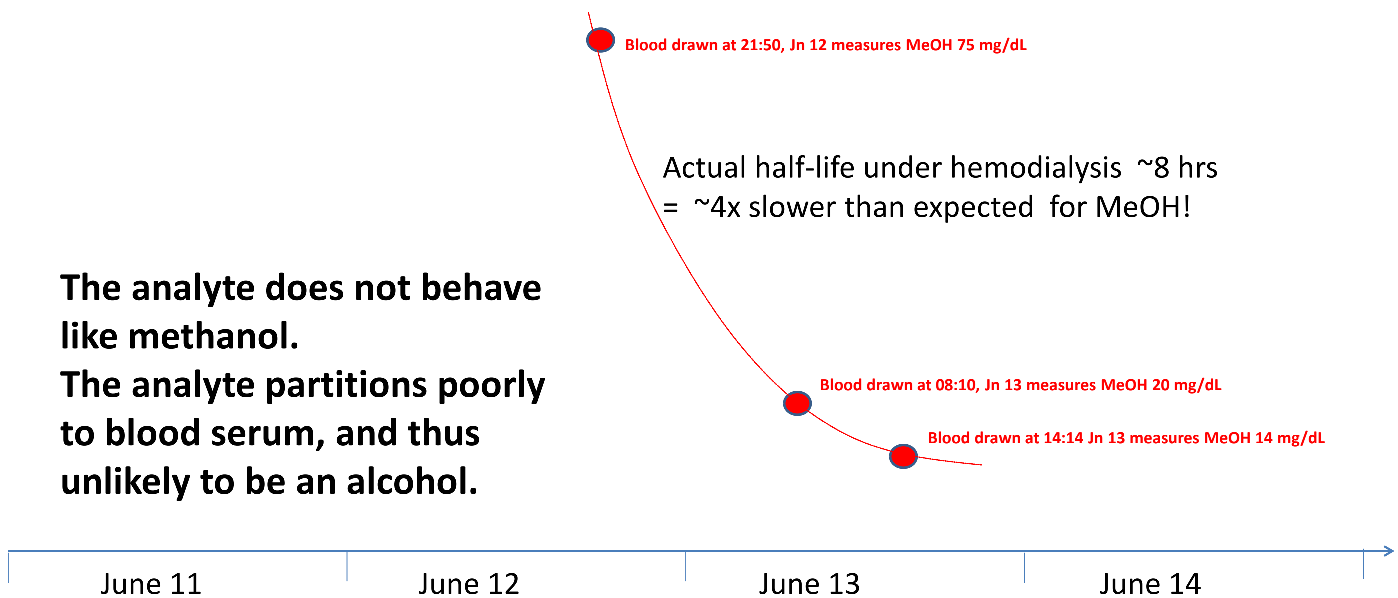


The pharmacokinetics reflect a ***discontinuit***y when the samples were analyzed by a different lab: an indicator of a false positive.

MeOH Pharmacokinetics are Discontinuous

Addition blood samples drawn at 23:00, 04:00 and 13:00, and sent to **LabCorp,** who reported **ZERO** methanol in all samples

What do the data indicate?



The analyte does not behave like methanol.
The analyte partitions poorly to blood serum, and thus unlikely to be an alcohol.

Nephrol Dial Transplant. 2010 May;25(5):1608-13. doi: 10.1093/ndt/gfp629. Epub 2009 Dec 17.

Methylamine clearance by haemodialysis is low.

Ponda MP[1], Quan Z, Melamed ML, Raff A, Meyer TW, Hostetter TH.

⊕ Author information

Is the DMPK behavior of the analyte consistent with any other chemical?

Abstract

BACKGROUND: Dialysis adequacy is currently judged by measures of urea clearance. However, urea is relatively non-toxic and has properties distinct from large classes of other retained solutes. In particular, intracellularly sequestered solutes are likely to behave differently than urea.

METHODS: We studied an example of this class, the aliphatic amine monomethylamine (MMA), in stable haemodialysis outpatients (n = 10) using an HPLC-based assay.

RESULTS: Mean MMA levels pre-dialysis in end-stage renal disease subjects were 76 +/- 15 microg/L compared to 32 +/- 4 microg/L in normal subjects (n = 10) (P < 0.001). Mean urea reduction was 62% while the reduction ratio for MMA was 43% (P < 0.01). MMA levels rebounded in the 1 hour post-dialytic period to 85% of baseline, whereas urea levels rebounded only to 47% of baseline. MMA had a much larger calculated volume of distribution compared to urea, consistent with intracellular sequestration. Measures of intra-red blood cell (RBC) MMA concentrations confirmed greater levels in RBCs than in plasma with a ratio of 4.9:1. Because of the intracellular sequestration of MMA, we calculated its clearance using that amount removed from whole blood. Clearances for urea averaged 222 +/- 41 ml/min and for MMA 121 +/- 14 ml/min, while plasma clearance for creatinine was 162 +/- 20 ml/min (P < 0.01, for all differences). Using in vitro dialysis, in the absence of RBCs, solute clearance rates were similar: 333 +/- 6, 313 +/- 8 and 326 +/- 4 ml/min for urea, creatinine and MMA, respectively. These findings suggest that the lower MMA clearance relative to creatinine in vivo is a result of MMA movement into RBCs within the dialyser blood path diminishing its removal by dialysis.

CONCLUSION: In conclusion, we find that, in conventional haemodialysis, MMA is not cleared as efficiently as urea or creatinine and raise the possibility that RBCs may limit its dialysis not merely by failing to discharge it, but by further sequestering it as blood passes through the dialyser.

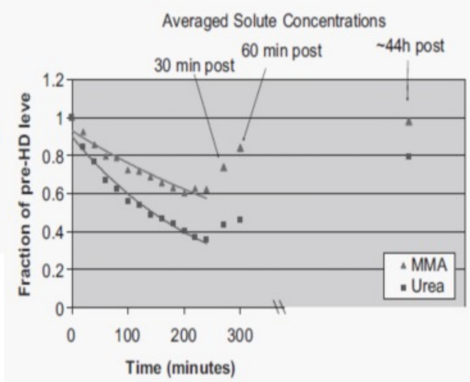


Fig. 1. The mean solute levels of MMA and urea throughout the course of haemodialysis, 30 and 60 minutes post-dialysis and prior to the next haemodialysis treatment (values are expressed as a fraction of the pre-dialysis, initial plasma level).

Methylamine's behavior under hemodialysis matches the analyte in Chuck Fleming's blood.