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Review Article

Bilateral Optic Neuropathy Following Methanol Ingestion: A Review of Published Cases

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Abstract

Background: Methanol poisoning causes acidosis and bilateral visual failure through its metabolite formate rather than through methanol itself, often after a latent interval when the patient appears well.

Objective: To set out which published variables predict blindness and death, and which treatments the record supports.

Methods: Narrative review of published outbreak cohorts, prospective and retrospective series and case reports.

Findings: In 38 prospectively studied patients, serum formate discriminated outcome with an area under the curve of 0.64 against 0.54 for serum methanol. In an ophthalmic series of 21 patients, mean blood methanol was higher in those without ocular symptoms. Admission arterial pH below 7.3 carried a risk estimate of 11.65 for chronic retinal nerve fibre layer loss in 42 survivors.

Conclusions: The published record supports decisions based on pH, base deficit and formate and early blockade of alcohol dehydrogenase; it does not support reassurance from a blood methanol concentration.

Keywords: Methanol poisoning; Optic neuropathy; Formate; Metabolic acidosis; Alcohol dehydrogenase inhibitors

Introduction

Methanol poisoning produces a clinical syndrome of severe metabolic acidosis, bilateral visual failure and, in the most severely affected, necrosis of the basal ganglia. Methanol itself is not the agent of this damage. It is oxidised by alcohol dehydrogenase to formaldehyde and then to formate, and it is formate that accumulates, consumes bicarbonate and injures the optic nerve. The consequence is a latent interval in which the patient may look well, followed by an abrupt and frequently irreversible loss of sight.

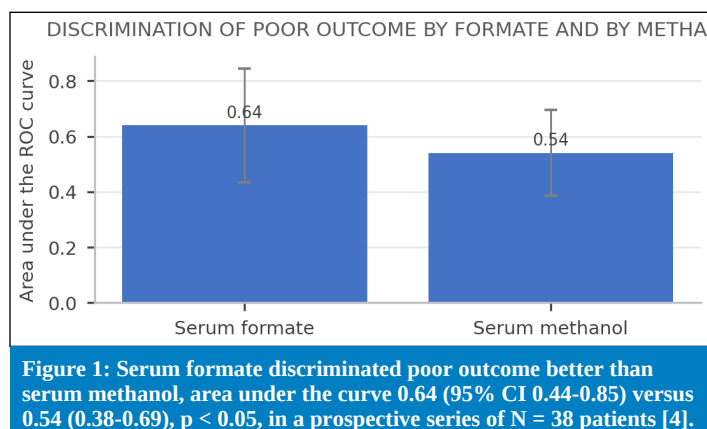
This article reviews the published record: outbreak cohorts, prospective and retrospective series, and individual published cases. It reports no patient of the present authors, and every clinical particular below is drawn from a named published report.

The argument advanced here is narrow and practical. The blood methanol concentration, the test clinicians instinctively order and trust, is among the weakest available predictors of blindness, while serum formate and arterial pH are among the strongest. In at least one published ophthalmic series the relationship runs in the opposite direction to intuition, with higher methanol concentrations in the patients whose eyes were spared. A methanol concentration that does not look alarming must therefore never be used to reassure. The treatment corollary follows directly: the intervention with a large and consistent published signal is early blockade of alcohol dehydrogenase, including before the patient reaches hospital, together with correction of acidosis, and the adjuvant therapies that dominate the recent ophthalmic literature rest on uncontrolled before-and-after observation [1,2].

Formate, Not Methanol, as the Proximate Toxin

The human evidence that formate causes the acidosis was established in two patients in whom formate was actually assayed rather than inferred. Both presented with the

established syndrome; arterial pH was approximately 6.9, plasma bicarbonate 3 mEq/L, and initial blood formate 11.1 to 26.0 mEq/L. The fall in bicarbonate matched the rise in formate in magnitude. Bicarbonate, ethanol infusion and haemodialysis returned blood formate to control values rapidly, and methanol fell less than formate did. Treatment succeeded in only one of the two patients [3]. That formate acts as a mitochondrial toxin, inhibiting cytochrome c oxidase within the retinal ganglion cell axons and the optic nerve, is the mechanism advanced in the review literature and is cited here as such rather than as a finding of this review [2].



The dose-response relationship between formate and outcome was measured prospectively in 38 patients during a mass poisoning. Median admission serum formate was 1.9 mmol/L (interquartile range 1.5 to 2.4) in asymptomatic patients, 15.2 mmol/L (13.9 to 17.6) in those with visual disturbance, 15.7 mmol/L (12.8 to 18.5) in those comatose on admission, 16.1 mmol/L (14.3 to 19.9) in those who went on to long-term visual sequelae and 15.2 mmol/L (13.8 to 15.9) in those who died. A formate concentration of 3.7 mmol/L or more was taken as sufficient to produce the first clinical signs of visual toxicity and as an indication for haemodialysis, while concentrations of 11 to 12 mmol/L and above were associated with visual and central nervous system sequelae and with death. The probability of a poor outcome exceeded 90% at formate of 17.5 mmol/L or

more, lactate of 7.0 mmol/L or more, or pH below 6.87 [4]. The discriminating step in that dataset is between asymptomatic and symptomatic patients rather than between symptom types.

Why a Reassuring Blood Methanol Level Misleads

In the same prospective series of 38 patients, serum formate discriminated outcome with an area under the receiver operating characteristic curve of 0.64 (95% confidence interval 0.44 to 0.85), against 0.54 (0.38 to 0.69) for serum methanol, a difference reported as significant at $p < 0.05$ [4]. Neither figure is impressive in absolute terms, but the ordering matters: the parent compound performs close to chance.

The inversion is clearer still in an ophthalmic series of 21 patients, 41 eyes, assessed after an outbreak in Tunisia. Eleven patients (52.4%) had ocular symptoms and 10 (47.6%) did not. Among the symptomatic, ocular abnormalities were found in 81.8%, comprising optic neuropathy in 7 (63.6%), central retinal artery occlusion in 1 (9.1%) and central serous chorioretinopathy in 1 (9.1%). Mean blood methanol was significantly higher in the patients without ocular symptoms than in those with them ($p = .03$) [5]. A concentration measured late, after much of the parent compound has already been converted, tells the clinician how much methanol remains, not how much formate has been generated.

Among 51 hospitalised confirmed cases in the Norwegian outbreak of 2002 to 2004, median serum methanol was 25.0 mmol/L with a range of 3.1 to 147.0 mmol/L, while median pH was 7.20 with a range of 6.50 to 7.50; visual disturbance was present in 55% and 24% were comatose on admission, of whom 67% died [6]. It was pH below 6.90 and a base deficit above 28 mmol/L, not the methanol concentration, that predicted poor outcome in that cohort.

Acid-Base Status as the Working Prognostic Variable

Acidosis has been the strongest predictor of both survival and vision in every cohort in which it has been tested. In a retrospective review of 122 patients from a cluster outbreak, of whom 121 were male and 10 died, pH was the strongest predictor of final visual acuity: the odds that a patient presenting with a pH above 7.2 would have only transient visual disturbance were 31 (95% confidence interval 6 to 149). Early presentation and treatment did not significantly alter visual outcome in severe poisoning [7]. In multivariate analysis of 101 hospitalised patients from the Czech outbreak of 2012, pH below 7.0 (odds ratio 0.04, 95% confidence interval 0.01 to 0.16, $p < 0.001$), negative serum ethanol (0.08, 0.02 to 0.37, $p < 0.001$) and coma on admission (29.4, 10.2 to 84.6, $p < 0.001$) were the independent determinants of death [8]. In a pooled multicentre dataset of 203 analysable patients from Norway, Estonia, Tunisia and two Iranian centres, of whom 48 died and 34 were discharged with neurological sequelae, pH below 7.00 was again the strongest risk factor for poor outcome, alongside a Glasgow Coma Score below 8 and inadequate hyperventilation [9].

Acidosis also predicts the chronic structural fate of the optic nerve. In 84 eyes of 42 survivors examined by optical coherence tomography at a mean of 4.9, 25.0 and 49.9 months after discharge, an admission arterial pH below 7.3 carried an age- and sex-adjusted risk estimate of 11.65 (95% confidence interval 1.91 to 71.12) for chronic global retinal nerve fibre layer loss. Abnormal retinal nerve fibre layer thickness was present in 13 of 42 (31%) and chronic axonal loss in 10 of 42 (24%), and 7 of those 10 had progressive visual loss [10].

Lessons from the Published Cases

The individual published records show how variable the presentation is and how poorly the acute picture forecasts the eventual outcome. Latency to visual symptoms depends on the route of exposure: in a series of eight patients it was 6 to 34 hours after ingestion, 3 to 4 months after inhalational exposure and more than 10 years in a

woman who had absorbed industrial alcohol percutaneously while using it as a hand detergent in pipeline work. Seven of the eight had optic nerve lesions on magnetic resonance imaging, and optical coherence tomography showed macular ganglion cell and inner plexiform layer thinning before peripapillary nerve fibre layer thinning. Seven of the eight improved transiently, and all eight ended with light perception or no light perception [11]. The commonly quoted latent interval of hours to a few days, prolonged by co-ingested ethanol, is textbook pharmacology rather than a measured distribution, and is attributed here to the review literature [1].

Table 1: Published cases of methanol-associated optic neuropathy reviewed here, with fields left as not stated where the published record is silent [3,12,25,5,11]; N = 5 reports covering 9 patients.				
Report	Age / sex	Exposure and latency	Presenting pH or methanol	Treatment and visual outcome
McMartin 1980, n=2	not stated	Ingestion; latency not stated	pH 6.9; formate 11.1-26.0 mEq/L	Bicarbonate, ethanol, dialysis; 1 of 2 survived
Yang 2005	Middle-aged man	Contaminated drink; latency not stated	not stated	not stated; profound vision loss, putaminal necrosis
Pakravan 2012, case 1	Adult, sex not stated	Ingestion; latency not stated	not stated	EPO, steroid, vitamins; 20/20 both eyes at 3 days
Pakravan 2012, case 2	35, male	Ingestion; treated within 1 week	not stated	Same regimen; CF at 6 ft right, 20/30 left at 2 weeks
Rym 2023, case A	20, male	Ingestion; seen on day 4	pH 7.3; methanol 0.07 g/L	No dialysis; 20/20 both, right RAPD and disc swelling
Rym 2023, case B	25, male	Ingestion; seen on day 4	pH 7.37; methanol 0.018 g/L	No dialysis; 20/25 right, 20/20 left, central serous CR
Sun 2022, patient 1	60s, male	Industrial alcohol ingested; 20 h	not stated	Corticosteroid; NLP both eyes at 42.6 months

Report	Age / sex	Exposure and latency	Presenting pH or methanol	Treatment and visual outcome
Sun 2022, patient 8	40s, female	Percutaneous; onset after 10 years	not stated	not stated; NLP both eyes from onset to last visit

Preserved Snellen acuity does not exclude structural injury. A 20-year-old man admitted four days after ingestion, with pH 7.3 and blood methanol 0.07 g/L and not dialysed, had 20/20 acuity in each eye five days after ingestion yet a right relative afferent pupillary defect, a swollen hyperaemic right disc and increased temporal nerve fibre layer thickness [5]. Conversely, the paradigm published case of the fully developed syndrome combined profound vision loss with severe brain damage and characteristic bilateral haemorrhagic necrosis of the putamen [12]. Late structural signs are common: in 50 consecutive patients examined in the chronic phase, cup-to-disc ratios of 0.8 or more were present in at least one eye of 22 (43 of 100 eyes), and increasing cupping correlated with worse acuity (p = 0.007) and with increasing age, but not with putaminal necrosis [13].

Outbreak Cohorts and the Burden of Permanent Visual Loss

In the Estonian outbreak of 2001, 147 patients were admitted with suspected poisoning and the diagnosis confirmed in 111, of whom 25 (23%) died in hospital; 43 further deaths occurred outside hospital, giving 154 cases and 68 deaths, an overall mortality of 44%. Twenty patients (18% of the 111 confirmed) survived with permanent sequelae, 18 with impaired vision and 3 with permanent brain damage. Ethanol was given to 87%, haemodialysis to 71%, bicarbonate to 85% and mechanical ventilation to 61% [14]. At six years, among the 86 hospital survivors, visual disturbance persisted in all four Group II patients examined, and apparently new visual complications were identified in 36% [15]. In the Czech outbreak of 2012 there were 121 confirmed poisonings, with 20 pre-hospital deaths and 101

hospitalisations, of whom 60 survived without sequelae, 20 survived with visual or central nervous system sequelae and 21 died; total mortality was 34% and hospital mortality 21% [8].

Table 2: Published methanol outbreak cohorts, with mortality and permanent visual loss as reported; cells marked not reported are absent from the published records [14,6,8,16,7,5,9]; N = 7 cohorts.				
Cohort	Year	N	Mortality	Permanent visual loss
Estonia	2001	154 (111 confirmed)	68 (44%); 25/111 (23%) in hospital	18/111 (16%) with impaired vision
Norway	2002-2004	51 hospitalised	9/51 in hospital; 17 in total	not reported; 55% visual disturbance at onset
Czech Republic	2012	121	41 (34%); 21/101 (21%) in hospital	20/101 (20%) visual and/or CNS sequelae
Czech follow-up subset	2012	50	not reported	20/50 (40%), including 8% blind
India, cluster outbreak	2013	122	10 (8%)	not reported
Tunisia	2023	21 assessed	not reported	optic neuropathy in 7/11 symptomatic (63.6%)
Pooled multicentre	1979-2010	203	48 (24%)	34 (17%) with neurological sequelae

The proportion with visual damage is systematically underestimated at discharge. In a 50-patient follow-up subset, 7 of 50 (14%) had recognised visual sequelae at discharge, yet 20 of 50 (40%) had long-term visual sequelae including 8% blindness; among those discharged without detected visual damage, 8 of 37 (22%) had abnormal nerve fibre layer and visual evoked potentials, and patients with visual sequelae had brain lesions more often (70% versus 27%, $p < 0.01$) [16]. Recovery, when it occurs, is early: of 37 followed survivors presenting with visual disturbance, 7 recovered fully within two weeks of discharge, 5 who were blind at discharge partially recovered within three to four weeks, and 5 blind at

discharge never improved at all [17].

What the Treatment Evidence Supports

Only one intervention shows a large and consistent published signal. Among 100 hospitalised confirmed cases in the Czech outbreak, 30 received out-of-hospital ethanol from paramedic or medical staff, with a median admission serum ethanol of 84.3 mg/dL (interquartile range 32.7 to 129.5). No patient with a positive admission serum ethanol died, against 21 deaths among those with negative ethanol, a mortality of 0% versus 36.2%; survival without visual or central nervous system sequelae was 90.5% versus 19.0% [18]. In the same outbreak, positive admission serum ethanol was associated with a 93% reduction in the odds of optic axonal damage (odds ratio 0.07, 95% confidence interval 0.01 to 0.8, $p < 0.05$) and pre-hospital ethanol with a 90% reduction in abnormal nerve fibre layer (0.10, 0.02 to 0.52, $p < 0.01$) [16]. Which blocking agent is used appears not to matter: in-hospital mortality was 16% with ethanol ($n = 70$) and 24% with fomepizole ($n = 21$), $p = 0.39$, and continuous haemodialysis (29%, $n = 45$) did not differ from intermittent haemodialysis (17%, $n = 30$), $p = 0.23$; folate affected neither mortality nor the probability of visual sequelae [8,19,20,21,22].

The adjuvant literature is weaker than its volume suggests. Erythropoietin has been reported in an uncontrolled series of 16 patients, in whom median better-eye acuity improved from light perception to 1.00 logMAR ($p < 0.0001$) [23], in 105 patients treated with erythropoietin plus methylprednisolone, in whom mean best-corrected acuity improved from 2.0 ± 0.86 to 1.39 ± 0.69 logMAR ($p < 0.001$) [24], and in earlier case and adjunctive reports [25,26]. Where a concurrent untreated group existed, in 9 patients and 18 eyes, final acuity was 1.32 ± 0.79 logMAR with erythropoietin against 1.36 ± 0.85 without, with no significant difference, and disc pallor in all eyes at final examination [27]. The steroid evidence is not merely weak but uninterpretable, because in every series located here

steroids were co-administered with erythropoietin or with ethanol [28,25,24,27]; no controlled trial isolates a steroid effect.

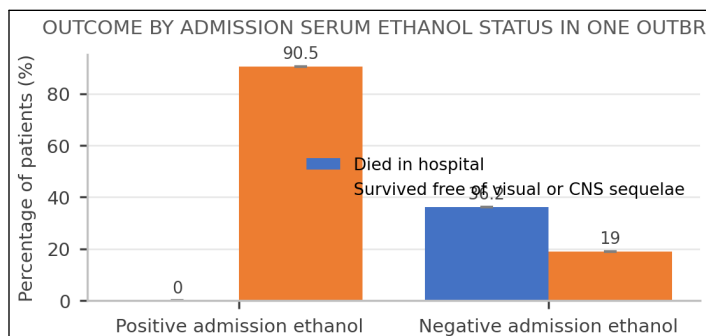


Figure 2: In-hospital mortality of 0% versus 36.2% and survival free of visual or central nervous system sequelae of 90.5% versus 19.0%, according to whether admission serum ethanol was positive or negative, among N = 100 hospitalised confirmed cases in one mass poisoning [18].

Conclusion

The published record supports a clear clinical position. Formate and acidosis, not the blood methanol concentration, determine whether a patient survives and whether that patient sees. A methanol level that appears unremarkable is compatible with severe and progressive optic neuropathy and has been measured as higher in patients whose eyes were spared, so it must never be used to withhold or delay treatment. The decisions that change outcome are made on pH, base deficit, formate where it is available, and the mental state of the patient, and they are made early: blockade of alcohol dehydrogenase before hospital arrival was associated with no deaths at all in the one outbreak where it was systematically compared. Visual damage should be sought actively at follow-up rather than assumed to have been recognised at discharge, since it is present in roughly twice as many survivors as the discharge record suggests.

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