Int J Leg Med (1992) 105:111–114

International Journal of
Legal Medicine

The elimination kinetics of methanol and the influence of ethanol

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Received January 6, 1992 / Received in revised form March 4, 1992

Summary. Four male subjects aged between 20 and 29 years were given intravenous injections of methanol at a dosage of 10 mg per kg body weight, once without prior administration of ethanol, and once after oral ingestion of 0.3 g ethanol per kg body weight. The serum methanol concentration was monitored over the next 5 h (after methanol administration alone) and 6–7 h (after methanol administration following ethanol ingestion). The elimination of methanol administered alone was found to follow first-order kinetics with a rate constant for the elimination phase of 0.475–0.259 h^{-1}, corresponding to an elimination half-life of 1.8–3.0 h. When ethanol was also administered methanol oxidation was found to be completely blocked until the blood ethanol concentration had fallen to 0.2 g/kg. When the ethanol concentration had dropped to zero, methanol elimination followed exactly the same course as that observed in the experiment without prior administration of ethanol (k: 0.378–0.231 h^{-1}; $t_{1/2}$: 1.5–2.7 h).

Key words: Elimination kinetics – Methanol – Human methanol elimination – Ethanol

Zusammenfassung. Vier männliche Probanden im Alter zwischen 20 Jahren und 29 Jahren wurden 10 mg Methanol pro Kilogramm Körpergewicht intravenös injiziert. Die Methanolapplikationen erfolgten einmal bei Ethanol-Nüchternheit, einmal nach vorangegangener oraler Zufuhr von 0,3 g Ethanol pro Kilogramm Körpergewicht. Der Verlauf der Serum-Methanolkonzentrationskurve wurde über 5 Stunden (alleinige Methanolzufuhr) bzw. 6 bis 7 Stunden (zusätzliche Ethanolzufuhr) beobachtet. Nach alleiniger Methanolapplikation folgte die Methanol-Elimination einer Funktion erster Ordnung mit terminalen Dispositionskonstanten zwischen 0,475 h^{-1} und 0,259 h^{-1}, entsprechend Eliminations-Halbwertszeiten von 1.8 h bis 3,0 h. Nach gleichzeitiger Ethanolzufuhr wurde die Methanol-Oxydation bis herab zu Ethanolkonzentrationen von 0,2 g/kg vollständig blockiert. Nach Erreichen der Ethanol-Nüchternheit zeigte die Methanol-Elimination keine Unterschiede im Vergleich zu den Versuchen ohne gleichzeitige Ethanolbelastung (k: 0.378 h^{-1} bis 0,231^{-1}; $t_{1/2}$: 1,5 h bis 2,7 h).

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Schlüsselwörter: Eliminationskinetik – Methanol – Mensch, Methanolelimination – Ethanol

Introduction

In recent years, methanol has taken on a new significance in forensic medicine, as it has done in psychiatry. It is of relevance in the evaluation of congeners for verification of statements concerning ingestion of alcohol [3] and may play a role in the diagnosis of alcohol abuse and alcoholism [13]. Detailed knowledge of the elimination kinetics of methanol in man is necessary for reliable interpretation of methanol levels. However, inconsistent findings concerning some of the most important points are quoted in the literature: for example, some authors describe the elimination of methanol as linear [16, 22, 23, 27, 29], while others describe it as exponential [1, 6, 17, 19, 20], and widely ranging values for the rate of elimination are quoted. The possibility has also been discussed that the elimination kinetics and rate are dependent on the order of magnitude of the blood methanol level, for example through saturation of the enzyme capacity as with ethanol and an increase in significance of purely physical processes of elimination, especially through the lungs, at higher concentrations [4, 11]. This study was undertaken to provide further information about the elimination kinetics of methanol at the lower concentrations (< 20 ppm) usually found in the situations mentioned above.

Materials and methods

The investigations were carried out on 4 healthy male subjects aged between 20 and 29 years who were all accustomed to moderate drinking. The amount of methanol given was chosen to achieve a C_0 value for serum methanol concentration of about 15 ppm. This level ensures a sufficiently long period over which the elimination kinetics can be investigated, while being well under the lowest concentration at which toxic effects can be expected (100 ppm [24]) and under the recommended tolerance level for long-term occupational exposure to methanol (30 ppm in urine, corresponding to about 22 ppm in blood [12]). The subjects were denied food and alcohol for 12 h, after which blood was taken and tested for endogenous methanol. Methanol, at a dosage of 10 mg per kg body

weight, was then infused intravenously over a period of 10 min. A 1% isotonic solution of methanol specially prepared by the university dispensary was used, its concentration being verified in our own laboratories before infusion. The subjects were not put at acute risk by the intravenous route of administration, since it is the oxidation products of methanol rather than methanol itself that are toxic, the rate of rise of the blood concentration thus being of no great importance. The next blood sample was taken 5 min after completion of the infusion; subsequent samples were taken over the next 5 h, initially every 15 min, then every 30 min, and finally at intervals of 1 h.

The investigations were continued 2 days later. This time, the subjects were given congener-free ethanol at a dose of 0.3 g per kg body weight to drink. After the blood ethanol level had started to rise, methanol was again infused at a dosage of 10 mg per kg body weight. Apart from the oral administration of ethanol, the experimental procedure was the same as that employed on the first day. However, the period of observation was extended to 6–7 h, depending on the time taken for the blood ethanol concentration to fall to zero.

Great care was taken to ensure that during the investigation none of the subjects ate fruit or any other foodstuffs that could have led to the ingestion of additional undetermined, but significant, amounts of methanol [10].

The serum methanol concentration was determined by gas chromatography (Hewlett Packard 5750; Carbopack B 5%), each sample being measured four times. Aqueous solutions, where appropriate with added ethanol, were used for calibration. The blood ethanol concentration was analyzed routinely in the alcohol laboratory using the methods set out by the German Public Health Department [21]: two measurements were obained enzymatically and two by gas chromatography.

Results

Figure 1 shows the serum methanol concentration-time curve, plotted on a semi-logarithmic scale, of Subject A after a single dose of methanol. The curve is biphasic, so that an open 2-compartment model can be assumed to apply [5]. The distribution phase is characterized by the residual line, which is obtained by subtracting the line of best fit through the points representing the elimination phase from the original data points. The distribution

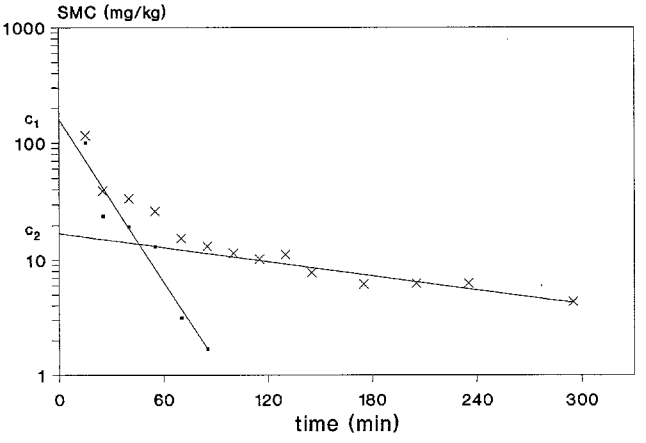

Fig. 1. Concentration-time profile of methanol elimination after single intravenous injection of methanol (10 mg/kg body weight) in Subject A. × = serum methanol concentration (SMC); • = residual line; c_1 = 140.2 mg/kg; c_2 = 16.9 mg/kg; $\lambda_1 = 2.903\,h^{-1}$; $\lambda_2 = 0.259\,h^{-1}$; $t_{½} = 2.7$ h

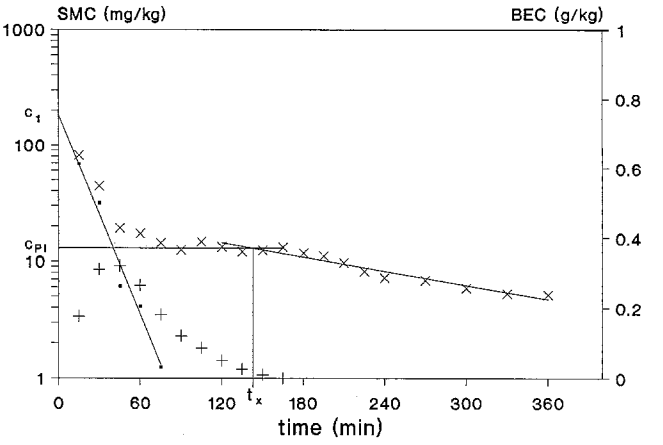

Fig. 2. Concentration-time profile of methanol elimination after intravenous infusion of methanol (10 mg/kg body weight) following oral ingestion of ethanol (0.3 g/kg body weight) in Subject A. × = serum methanol concentration (SMC); • = residual line; + = blood ethanol concentration (BEC); c_1 = 185.3 mg/kg; c_{pl} = 12.9 mg/kg; $\lambda_1 = 4.013\,h^{-1}$; $\lambda_2 = 0.276\,h^{-1}$, $t_{½} = 2.5$ h

phase generally lasted 60–90 min, but was a little longer in Subject A. Each subject could be assumed to be in a virtually pure elimination phase 2 h after the commencement of methanol infusion. Data pertaining to elimination kinetics were calculated only after this point, even when the curve was previously linear.

The elimination curves could be interpreted in terms of both zero-order kinetcis ($c_t = c_0 + \beta t$) and first-order kinetics ($c_t = c_0 e^{-kt}$) but the measured values showed a better fit in all cases with the first-order function than with the zero-order function (method of least squares). The results obtained on the second day of the experiment, as shown below, also indicated that first-order kinetics apply here. Thus, methanol elimination could be assumed to be exponential. The following equations were established for methanol elimination in the individual probands:

Subject A: $c_t = 16.9\,\text{mg/kg} \times e^{-0.259t}$
Subject B: $c_t = 16.5\,\text{mg/kg} \times e^{-0.325t}$
Subject C: $c_t = 14.8\,\text{mg/kg} \times e^{-0.406t}$
Subject D: $c_t = 17.8\,\text{mg/kg} \times e^{-0.475t}$

Values of 0.70–0.86 were derived for the distribution factor r from the c_0 values (serum concentrations converted to blood concentrations). The elimination half-life was found to range from 1.5 h to 2.7 h.

Figure 2 shows the results of the second experiment – the elimination of methanol after simultaneous administration of ethanol – again with the example of Subject A. The serum methanol concentration-time curve plotted on a semi-logarithmic scale is seen above, and the blood ethanol concentration-time curve, plotted on an arithmetic scale using the same time axis, is seen below. After a 60–90 min distribution phase, the methanol curve formed a plateau, which extended into the end phase of ethanol elimination. Thereafter methanol concentration decreased exponentially.

The shape of the methanol curve can be explained by the blocking of methanol oxidation by ethanol, which is

exploited in the treatment of methanol intoxication [26]. The distribution phase and elimination phase do not overlap as they do in the classical 2-compartment model. The first part of the curve is determined almost exclusively by the process of distribution. Methanol elimination through the lungs and kidneys – about 1% at these concentrations according to Leaf and Zatman [20] – can be ignored, for such short periods of time as can endogenous production of methanol in the course of intermediary metabolism, which amounts to far less than 0.5 ppm/h [2, 9, 14, 15]. The end of the distribution phase is reflected in the commencement of the plateau, which represents the concentration when distribution is complete but elimination has not yet commenced, and therefore corresponds approximately to the theoretical c_0 value. However, in the following it will be referred to, more correctly, as c_{pl}.

The methanol concentration-time curve was evaluated firstly by determination of the line of best fit through the points representing the elimination phase, starting with the second measurement after the ethanol concentration had fallen to zero. The value of c_{pl} was estimated from the mean of the values lying on the plateau of the curve, an interval of one value being left for accuracy after the end of the distribution phase and before the onset of the elimination phase. The point t_x on the time axis where the elimination line intercepts the plateau ($c_{tx} = c_{pl}$) was taken as $t_x = 0$. Elimination can then be described by the equation $c_t = c_{pl}\, e^{-kt}$. For the individual subjects, then:

Subject A: $c_t = 12.9\,\text{mg/kg} \times e^{-0.276t}$
Subject B: $c_t = 18.0\,\text{mg/kg} \times e^{-0.231t}$
Subject C: $c_t = 15.3\,\text{mg/kg} \times e^{-0.378t}$
Subject D: $c_t = 14.5\,\text{mg/kg} \times e^{-0.300t}$

Values of 1.8–3.0 h were calculated for the elimination half-life from the above. If c_{pl} is taken as equal to c_0, the distribution factor r would range from 0.70 to 0.97. No major differences were found between these results and those of the experiment in which there was no prior administration of ethanol.

The second part of the experiment, in addition to providing information about the elimination kinetics of methanol, gives some indication of the time of onset of methanol oxidation during the end-phase of the blood ethanol curve. Cessation of enzyme inhibition probably occurs approximately at time t_x, at which the plateau and elimination line intersect. The blood ethanol concentration at t_x, as read from the ethanol curve, was found to be 0.02 g/kg, 0.11 g/kg, 0.00 g/kg and 0.03 g/kg, respectively, for the 4 subjects.

Discussion

Our results show that the elimination of methanol in man at concentrations less than 20 ppm follows an exponential rather than a linear course, with an elimination half-life of 1.5–3 h. These results are well in accordance with those of Leaf and Zatman [20], Kendal and Ramanathan [19] and Dutkiewicz et al. [6]. These researchers studied the elimination kinetics of methanol by monitoring urinary excretion of methanol at concentrations of 20–70 ppm achieved by oral administration. Elimination half-lives of about 3 h and 1.5 h can be calculated from the formulae described by Leaf and Zatman and by Dutkiewicz et al., respectively. Although Kendal and Ramanathan do not give a formula for elimination, the decline in concentration illustrated is clearly exponential, and the elimination half-life can be estimated at about 2 h.

Neither our results nor those of Kendal and Ramanathan have provided any evidence that prior blocking of methanol oxidation by ethanol exerts an influence on the rate of subsequent methanol elimination. Acceleration of elimination, as observed by Rietbrock [25] at toxic concentrations in dogs after intermittent administration of ethanol, was not noted. Findings published by Jones [17] are of interest for comparison here: in this study, the subjects were given alcoholic beverages with a high methanol content, producing peak methanol concentrations of about 10 ppm. Values obtained for the elimination half-life – calculated from the methanol concentration in expired air – were found to range from 1.8 h to 3.5 h.

Zero-order elimination kinetics have been reported in rare cases of methanol intoxication where neither dialysis nor ethanol administration were used as treatment. Jacobsen et al. [16] described a case in which elimination was linear (elimination rate of 85 ppm/h), whereas Martensson et al. [23] assumed, without verification, that elimination was linear (elimination rate of about 30 ppm/h). Kane et al. [18] presented, without further investigation of the kinetics, 5 concentration time curves, some of which appear to be linear and some exponential. However, the initial methanol concentrations in all these cases of intoxication were so high that it is impossible to draw conclusions from the results about the situation at the low levels of interest here.

Majchrowicz and Mendelson [22] have published observations concerning low concentrations in alcoholics. Although these authors quote an elimination rate of 2.9 ppm/h, indicating linear elimination, they declare themselves to be in agreement with Leaf and Zatman [20], who had, in fact, described elimination as following an exponential course. The 2 curves included in the article by Majchrowicz and Mendelson seem to indicate first-order kinetics.

Schmutte et al. [27] and Urban et al. [29] both undertook investigations of relevance to congener analysis, and both reported that the elimination of methanol follows a linear course. Schmutte et al. monitored the blood methanol concentration after oral ingestion of methanol. However, only 3 values (including the peak value) in the 45 min following attainment of the peak concentration were available for interpretation. Even disregarding the fact that absorption of methanol from the intestinal tract is relatively slow [8, 20, 28], thus preventing inclusion in the calculations of the first value after the peak of the curve, the experimental design allows no conclusions about the elimination kinetics of methanol to be drawn. Maximum concentrations of only 2–4 ppm were achieved by the consumption of alcoholic

beverages in the subjects included in the study conducted by Urban et al. [29]. Thus here, too, elimination could be followed for only a short period, and blood levels were close to the endogenous concentration of methanol [7, 9, 15, 17, 27]. It would therefore seem to be difficult to draw any definite conclusions about methanol elimination kinetics from these results.

In addition to providing information about the elimination kinetics of methanol, our investigations also give some indication as to when methanol oxidation commences after blocking by ethanol. Taking into account variants deriving from the experimental method and analysis, and the gradual transition from the plateau phase to the elimination phase, it is possible to say that methanol oxidation probably does not begin until the blood ethanol concentration has fallen to at least 0.2 g/kg. This is well in accordance with the findings of Iffland et al. [14, 15] and Urban et al. [29]. Barz et al. [1] reported that methanol elimination commences at a blood ethanol concentration of 0.5 g/kg, however, these authors took blood samples at intervals of 2 h, corresponding to a change in blood ethanol concentration of about 0.3 g/kg, so that this observation is likely to be associated with a wide margin of error.

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