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Case Report

Pharmacokinetic analyses using absorption kinetics in low-alcohol dose cases of drunken driving

Ayako Himemiya-Hakucho*, Tatsuya Fujimiya

Department of Legal Medicine, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi 755-8505, Japan

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ABSTRACT

In Japan, low-alcohol dose cases of drunken driving, where drivers drink just before getting behind the wheel, are increasing for expert witnesses since the penalties for drunken driving have become stricter. Widmark's equation has generally been used for the pharmacokinetic analysis of blood alcohol concentration, which encompasses the one-compartment model with zero-order elimination kinetics but ignores absorption kinetics. We therefore propose that the formula might not be applicable to the analysis of low-alcohol dose cases of drunken driving because the issue is focused on the absorption phase. In this paper, we present two representative low-alcohol dose cases, which were analyzed using the one-compartment model with first-order absorption and zero-order elimination kinetics. This formula is thought to be more suitable and useful for medicolegal practice than Widmark's formula.

1. Introduction

In Japan, driving a car under the influence of alcohol (DUI) is a large social problem. Since the 2000s, many horrific fatal accidents caused by drunken drivers have resulted in people demanding stricter laws, and repeated revisions to sections of the Road Traffic Act have seen harsher penalties for drunken driving being introduced and enforced. As a result of these stricter changes, the rate of fatal accidents caused by drunken drivers has decreased, whereas low-alcohol dose cases of drunken driving are still being registered [1–3]. Some of these cases have been difficult to prove in courts of law, and, consequently, the police or the public prosecutor has often consulted us to carry out pharmacokinetic analysis.

In general, Widmark's equation has been used for the estimation of blood alcohol concentration (BAC) when forensic pathologists offer interpretations of what constitutes drunken driving. However, this formula relates to the one-compartment model with zero-order elimination kinetics, and it ignores absorption kinetics [4]. It is therefore our opinion that the formula may not be applicable to analyzing the low-alcohol dose case of a drunken driver who consumed alcohol just prior to operating the vehicle, because the issue is focused on the absorption phase. As a result of stricter changes in traffic law, low-dose cases and cases relating to the absorption phase have increased in Japan. In this report, we present two representative low-alcohol dose cases that relate to the absorption phase, which were analyzed using the one-compartment model with first-order absorption and zero-order elimination kinetics (the first-order absorption kinetic model) [5,6].

2. Pharmacokinetic analyses

BACs were estimated from noninvasive breath alcohol concentration (BrAC) measurement and the equations used were as below [5,6].

Widmark's equation: $C = D/Vd - \beta \times t$

First-order absorption kinetic model: $C = D/(Vd/F)[1 - exp(-ka \times t)] - \beta \times t$

where C (mg/mL) is the BAC at time t, D (g/kgBW) is the dose of alcohol ingested, Vd (L/kgBW) is the distribution volume, β (mg/mL/h) is the zero-order elimination rate constant, t is time in minutes, F is bioavailability, and k_a (/h) is the absorption rate constant.

These parameters were estimated using the weighted, non-linear, least-squares method, but the estimated initial values were determined via linear regression analysis. We simulated the cases using spreadsheet software of Microsoft Excel on a microcomputer (LAVIE, NEC Corporation, Tokyo, Japan). In accordance with previous studies [5,6], we carried out the analysis using the following values: $F = 1$, $Vd = 0.7$, $\beta_{60} = 0.16$ or 0.20, $k_a = 5$–15, which are estimated from standard Japanese values with respect to the ability of subjects to metabolize alcohol [7,8]. Bioavailability (F) is usually 1 unless the peak BAC is less than approximately 0.4 mg/mL, which indicates unsaturated capacity-limited metabolism of ethanol and low hepatic bioavailability [5,6]. Currently, the maximum alcohol level permitted by the

* Corresponding author at: Department of Legal Medicine, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan.
E-mail address: haku.a@yamaguchi-u.ac.jp (A. Himemiya-Hakucho).

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Road Traffic Act is 0.15 mg/L of breath. Since a plasma/breath ratio of 2000:1 is typically used, a BAC of 0.3 mg/mL is considered the legal limit [2,3].

3. Case reports

3.1. Case 1

A male suspect (body weight of 60 kg) caused a traffic accident at 0:50 p.m. He drank a 500 mL alcoholic beverage with 8% ethanol content at his home at 1:40 p.m., and his BrAC was then measured by the police at 2:00 p.m. The measured BrAC was 0.75 mg/L, and his BAC was calculated to be 1.5 mg/mL. He had a conviction for drunken driving but insisted that he had not been drinking when the traffic accident occurred. The police consulted us regarding the BAC associated with the accident, and we estimated its time-course using Widmark's formula and the first-order absorption kinetic model to assess which was more effective.

Our simulation presumed the subject had drunk the alcoholic beverage at 1:40 p.m. As a result, when β_{60} values were 0.16 and 0.20, the calculated BAC values at 2:00 p.m. were 0.70 and 0.68 mg/mL, respectively, using Widmark's formula, but only 0.56 and 0.54 mg/mL, respectively, using the first-order absorption kinetic model (Fig. 1). The values obtained using the latter method were lower than those seen using the former method, but these lower values seemed more appropriate because the time of BrAC measurement coincided with the absorption phase. With the actual measured BrAC, the BACs at 1:40 p.m. were calculated to be 0.80 and 0.82 mg/mL using Widmark's formula, but 0.94 and 0.96 mg/mL using the first-order absorption kinetic model when β_{60} values were 0.16 and 0.20, respectively (Fig. 2). These results suggest that alcohol was present in the subject's blood before he drank the alcoholic beverage at 1:40 p.m. as otherwise he would have had to drink three times as much, which seems improbable

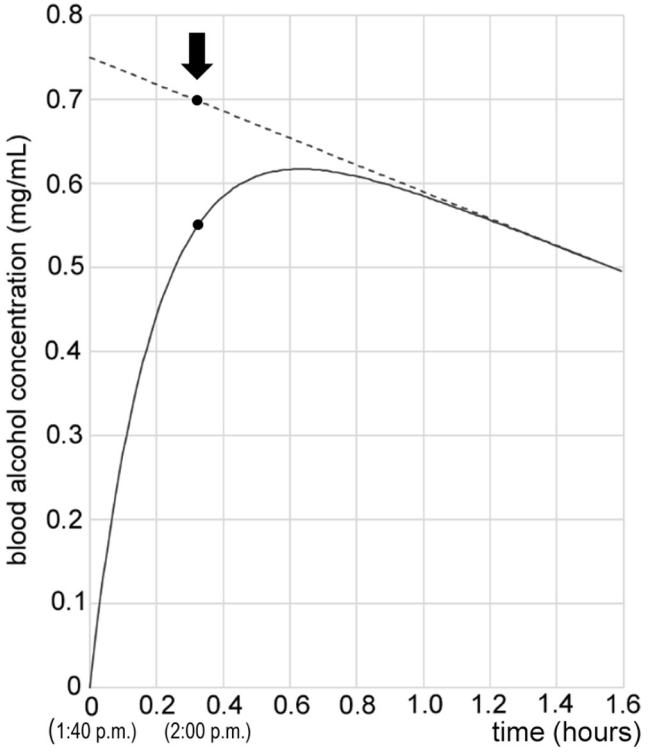

Fig. 1. Estimation of the time-course of BAC when the β_{60} value was 0.16 for Case 1. This is presuming the subject had drunk the alcoholic beverage at 1:40 p.m. (0 h in this Figure). The calculated BAC values at 2:00 p.m. (black arrow) were 0.70 mg/mL using Widmark's formula (- -●- -) but 0.56 mg/mL using the first-order absorption kinetic model (–●–).

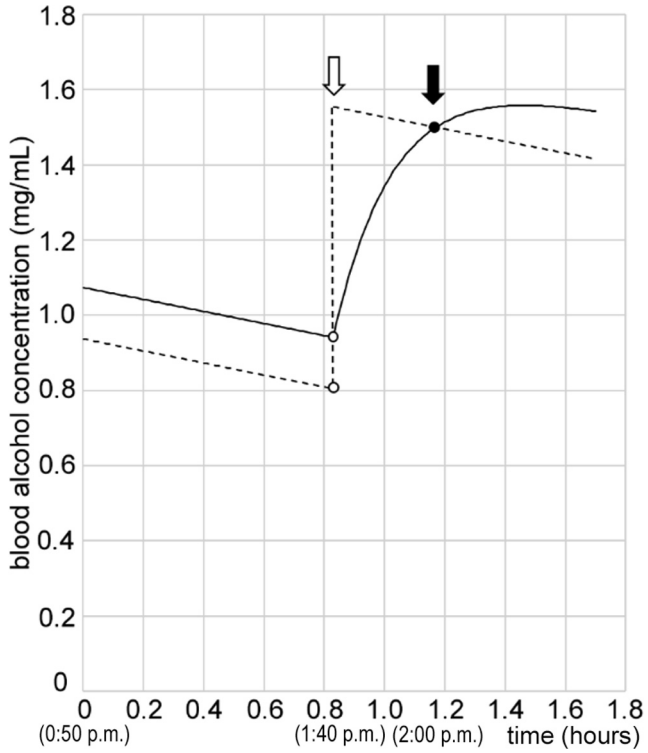

Fig. 2. Estimation of the time-course of BAC when the β_{60} value was 0.16 for Case 1. This was based on the actual value measured at 2:00 p.m. (black arrow). The calculated BAC values at 1:40 p.m. (white arrow) and at 0:50 p.m. (0 h in this Figure) were 0.80 mg/mL and 0.94 mg/mL using Widmark's formula (- -○- -) but 0.94 mg/mL and 1.07 mg/mL using the first-order absorption kinetic model (–○–).

within this short time period. Finally, we conducted a simulation based on both of the above-mentioned points. As a result, the BACs at 0:50 p.m. were calculated to be 0.94 and 0.98 mg/mL using Widmark's formula but were 1.07 and 1.12 mg/mL using the first-order absorption kinetic model, when β_{60} values were 0.16 and 0.20, respectively (Fig. 2).

From these results, we concluded that the subject had drunk alcohol and driven at the time of the traffic accident. With our expert testimony, he admitted his drunken driving.

3.2. Case 2

A male suspect (body weight of 75 kg) driving his car was stopped at a sobriety checkpoint by the police at 6:00 p.m. The police asked him to allow measurement of his BrAC because his breath smelled of alcohol, but he persistently refused to comply. Approximately 20 min after the time he was stopped, he eventually permitted measurement of his BrAC, which was 0.25 mg/L, and the BAC was calculated to be 0.5 mg/mL. He insisted that his act did not constitute drunken driving and maintained that his BrAC must have been less than the maximum permissible limit of 0.15 mg/L immediately after being stopped because he had drunk alcohol approximately half an hour prior to arriving at the checkpoint. He seemed to have drunk a 109 mL alcoholic beverage with a 40% ethanol content between 5:30 and 5:50 p.m. We were consulted by the public prosecutor regarding the BAC at the time the suspect had been stopped, and we estimated its time-course using Widmark's formula and the first-order absorption kinetic model while changing the settings of the β_{60} and k_a values.

We simulated the time-course of the BAC while changing the theoretical time drinking had been initiated to (for example) 5:40 p.m., the midpoint of the actual drinking phase which took place between 5:30 and 5:50 p.m. From these results, Fig. 3 and Fig. 4 show the time-course of the simulated BAC using the first-order absorption