

Post-Intervention Kinetics of Hydrogen Gas Inhalation: Influence of Variable Exposure Durations

Running Head: Pharmacokinetics of Hydrogen Gas

Sergej M. Ostojic^{1,2,*}, Nikola Todorovic³, David Nedeljkovic⁴, Jovana Panic⁵,
Teona Teodora Borovic⁵, Milan Vranes⁵

¹Faculty of Health Sciences, University of Pécs, Hungary

²Department of Nutrition and Public Health, University of Agder, Norway

³Faculty of Sport, University of Ljubljana, Slovenia

⁴Faculty of Sport and Physical Education, University of Novi Sad, Serbia

⁵Faculty of Sciences, University of Novi Sad, Serbia

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Abstract Molecular hydrogen (dihydrogen) has emerged as a promising therapeutic gas with potential benefits for treating various acute and chronic diseases. However, understanding its pharmacokinetics, especially in humans, remains limited. This pilot study aims to assess the pharmacokinetics of inhaled dihydrogen in healthy humans, focusing on the effects of varying exposures on blood dihydrogen concentrations. Five healthy male participants underwent three separate inhalation sessions (15, 30, and 45 minutes) of dihydrogen, with blood levels measured at multiple time points after inhalation. Pharmacokinetic analysis revealed significant differences in the time to maximum concentration (T_{max}) and the area under the concentration-time curve (AUC) across the different inhalation durations. A 45-minute exposure resulted in a lower T_{max} and a higher AUC, indicating more substantial systemic dihydrogen exposure. The minimum effective concentration (MEC) of blood dihydrogen following intervention was estimated to fall within the range of 0.42 to 1.05 $\mu\text{g/L}$. Our findings suggest a dose-response relationship between inhalation duration and hydrogen absorption, offering insights into the optimal dosing and timing for therapeutic applications of inhaled dihydrogen. The study provides preliminary

pharmacokinetic data essential for refining dihydrogen-based treatments in clinical settings.

Keywords Dihydrogen, Pharmacokinetics, Area under the Curve, Minimal Effective Concentration

1. Introduction

Molecular hydrogen (dihydrogen; H_2) is a novel medical gas that has garnered significant attention in medical and clinical research due to its potential therapeutic properties. Studies suggest that dihydrogen inhalation may mitigate oxidative stress, improve outcomes in ischemia-reperfusion injuries, and regulate cellular signaling pathways associated with cardiometabolic and neurodegenerative diseases (for a detailed review, see [1] and [2]). Despite promising evidence, numerous aspects of dihydrogen inhalation in human medicine remain insufficiently explored, particularly its pharmacokinetics, which is critical for establishing optimal dosing regimens and defining therapeutic windows. Preliminary studies

suggest that the therapeutic efficacy of dihydrogen may depend on exposure duration [3], making it crucial to understand its concentration dynamics across varying intervals to refine clinical applications and optimize therapeutic protocols. Most pharmacokinetic studies involving inhalational hydrogen have been conducted in animal models [4,5], limiting the direct applicability of their findings to human physiology. Human studies assessing how hydrogen gas is absorbed, distributed, metabolized, and eliminated are essential to advancing its clinical use. This pilot study aims to evaluate the pharmacokinetics of hydrogen gas inhalation in healthy humans, focusing on the effects of variable exposure durations on blood hydrogen concentrations. Findings from this research will provide a foundation for optimizing hydrogen-based therapeutic strategies and understanding its potential applications across different medical conditions.

2. Methods

Five healthy male participants (mean age 30.6 ± 4.4 years) provided written informed consent to voluntarily participate in this open-label, quasi-experimental, interventional pilot study. All individuals were free from acute injuries and major chronic conditions, including respiratory disorders that could impede the effective delivery of inhalational gas. Furthermore, participants refrained from the use of enteral, parenteral, or topical dihydrogen for at least one week prior to the study. The study protocol involved three separate laboratory visits, during which participants underwent a single session of continuous dihydrogen inhalation lasting 15, 30, or 45 minutes, with 7-day washout periods between interventions to mitigate potential carryover effects. The treatment protocols adhered to established safety standards for dihydrogen administration in various health contexts [6-8]. Dihydrogen gas was delivered via a facemask using a biological gas supply device (MIZ Company Ltd., Kanagawa, Japan) at a constant flow rate of 45 mL (3.77 mg) per minute, mixed with ambient air to ensure safety and tolerability. The apparatus was calibrated to maintain a consistent gas flow during each session. To standardize baseline metabolic conditions, participants underwent an overnight fast prior to laboratory visits. During each lab session, blood hydrogen levels were monitored, and participants were observed for potential adverse effects. Blood samples were collected at baseline (prior to inhalation), immediately upon cessation of inhalation (0 minutes), and at 5, 15, 30, 45, 60, 90, and 120 minutes post-inhalation during each session. Dihydrogen concentrations in the blood were measured immediately after sample collection using a highly sensitive Clark-type hydrogen micro-sensor (Unisense A/S, Aarhus, Denmark). This method allowed the detection of a stable hydrogen signal, ensuring that the measured concentrations reached a

plateau for accurate and reproducible assessments. The sampling timeframe was carefully managed to minimize the risk of blood coagulation, which could interfere with sensor function and compromise measurement accuracy. The hydrogen sensor was calibrated before each measurement using a standardized gas mixture (Messer Tehnogas AD, Belgrade, Serbia) to ensure precise readings. Additionally, the system was thoroughly cleaned and flushed before each test to maintain optimal performance and prevent cross-contamination between samples. Participants were also requested to report any side effects (e.g., dizziness, nausea, headache, dyspnea) experienced due to either intervention using an open-ended questionnaire. Data collection took place between November and December 2024, and the study protocol was approved by the local Institutional Review Board (# 9-09-14/2023-2) in compliance with ethical guidelines governing research involving human participants, ensuring the integrity and ethical conduct of the study procedures. Pharmacokinetic parameters for each participant and intervention protocol were calculated using a non-compartment extravascular solver based on the linear trapezoidal method [9]. The normality of data distribution was evaluated using the Shapiro-Wilk test. Variations in blood hydrogen levels for each intervention were assessed using the Kruskal-Wallis test, with Bonferroni correction applied to adjust for multiple comparisons. For the comparison of pharmacokinetic indices among the three interventions, one-way ANOVA was applied to normally distributed data, while the Kruskal-Wallis test was used for non-normally distributed data. Post hoc analyses included the Tukey test for one-way ANOVA and the Dunn test for the Kruskal-Wallis test. Statistical significance was set at $P < 0.05$. Data analysis was conducted using SPSS statistical software, version 24.0 for Mac (IBM SPSS Statistics, Chicago, IL, USA).

3. Results

All participants completed the study, and no adverse effects were observed or reported during any of the intervention sessions. The baseline blood dihydrogen concentration, measured prior to inhalation, was $0.21 \pm 0.06 \mu\text{g/L}$. The total amounts of dihydrogen administered during the 15, 30, and 45-minute intervention sessions were 56.6 mg, 113.1 mg, and 169.7 mg, respectively. Blood dihydrogen dynamics across three intervention protocols are illustrated in Figure 1. Blood hydrogen levels demonstrated a non-significant alteration following the 15-minute ($P = 0.055$) and 30-minute ($P = 0.068$) inhalation protocols. In contrast, the 45-minute inhalation protocol significantly affected blood hydrogen levels ($P = 0.001$), with concentrations markedly higher than baseline immediately post-inhalation ($P < 0.001$), as well as at 5 minutes ($P < 0.001$), 15 minutes ($P = 0.001$), and 30 minutes ($P = 0.001$) following cessation of inhalation.

Pharmacokinetic analysis revealed no significant differences across the three inhalation protocols for most indices, with two exceptions: time to maximum serum concentration ($P = 0.011$) and the area under the concentration-time curve up to the last quantifiable time point ($P = 0.041$) (Table 1). Post-hoc analysis indicated a

significantly longer time to maximum serum concentration in the 30-minute protocol compared to the 45-minute protocol ($P = 0.039$), and a significantly higher area under the curve in the 45-minute protocol compared to the 15-minute protocol ($P = 0.008$).

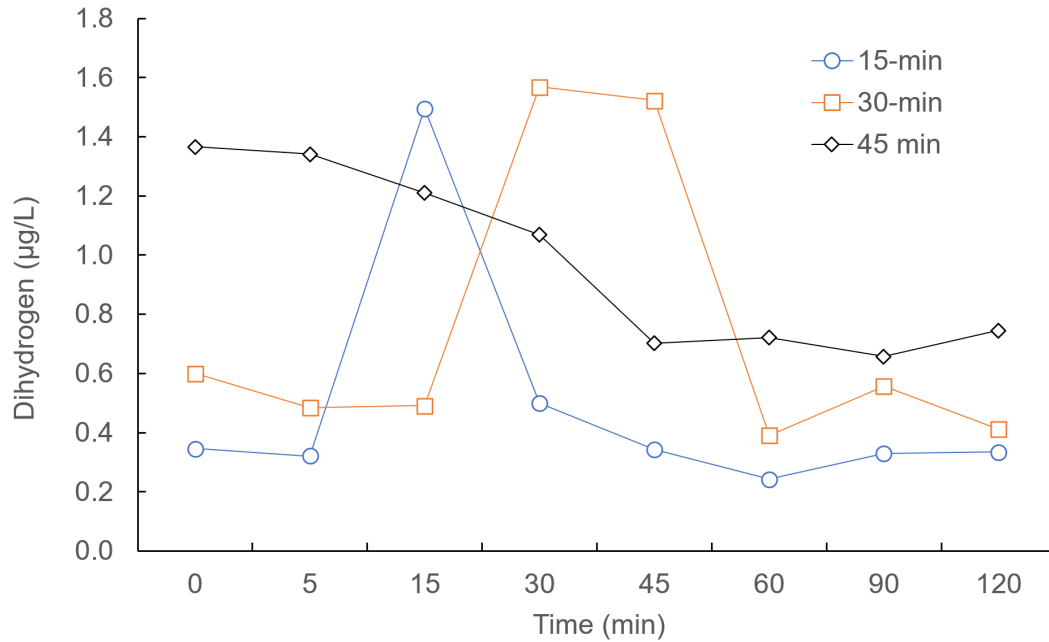


Figure 1. Blood dihydrogen levels during three inhalational protocols (error bars excluded for clarity)

Table 1. Pharmacokinetics indices during the study. Values are mean \pm SE

Parameter	Unit	Dihydrogen inhalation		
		15-min	30-min	45-min
Lambda _z	1/min	0.011 \pm 0.003	0.009 \pm 0.002	0.005 \pm 0.001
T 1/2	min	93.4 \pm 35.0	101.9 \pm 28.7	153.8 \pm 35.3
T max †	min	18.0 \pm 3.0	33.0 \pm 5.6 ‡	8.0 \pm 3.0 ‡
C max	µg/L	1.50 \pm 0.46	2.83 \pm 0.95	1.73 \pm 0.26
T lag	Min	0	0	0
C last_obs / C max	-	0.31 \pm 0.12	0.21 \pm 0.08	0.47 \pm 0.10
AUC 0-t †	µg/L·min	55.0 \pm 8.1 ‡	89.3 \pm 16.9	102.3 \pm 8.5 ‡
AUC 0-inf_obs	µg/L·min	116.9 \pm 44.7	159.5 \pm 40.7	276.4 \pm 47.0
AUC 0-t/0-inf_obs	-	0.61 \pm 0.12	0.62 \pm 0.09	0.42 \pm 0.09
AUMC 0-inf_obs	µg/L·min ²	26.1 \pm 18.8	27.8 \pm 12.2	74.9 \pm 30.3
MRT 0-inf_obs	Min	145.1 \pm 53.1	147.8 \pm 39.0	234.1 \pm 55.1
Vz/F_obs	(mg)/(µg/L)	70.5 \pm 15.1	105.3 \pm 18.7	132.6 \pm 15.2
Cl/F_obs	(mg)/(µg/L)/min	0.71 \pm 0.17	0.89 \pm 0.19	0.68 \pm 0.10

Abbreviations: Lambda-z, apparent terminal elimination rate constant; T 1/2, apparent terminal elimination half-life; T max, time to maximum blood concentration; C max, maximum blood concentration; T lag, time delay; C last_obs/C max, observed concentration at $t = t_{last}$ divided by C max; AUC 0-t, area under the curve up to the last quantifiable time point; AUC 0-inf_obs, observed area under the serum concentration-time curve extrapolated from time zero to infinity; AUMC 0-inf_obs, area under the moment curve extrapolated from time zero to infinity; MRT 0-inf_obs, mean residence time extrapolated from time zero to infinity; Vz/F_obs, apparent volume of distribution during the terminal elimination phase; Cl/F_obs, apparent total clearance of dihydrogen from the serum. The dagger (†) indicates statistically significant differences identified by one-way ANOVA (for AUC 0-t) and the Kruskal-Wallis test (for T max) across the protocols; double dagger (‡) denotes the specific protocols that differ significantly ($P < 0.05$).

4. Discussion

This pilot study represents a novel exploration of varying inhalational hydrogen exposure protocols in healthy humans. Our findings indicate that a 45-minute exposure to inhaled dihydrogen, delivering approximately 170 mg of hydrogen gas, exhibits distinct pharmacokinetic characteristics compared to shorter protocols. Specifically, this protocol resulted in a reduced time to reach maximum serum dihydrogen concentration and a larger area under the curve, signifying enhanced systemic exposure to hydrogen. These observations underscore a dose-response relationship, highlighting the critical influence of exposure duration (and cumulative dose) on systemic hydrogen turnover.

Only a limited number of animal studies have investigated the pharmacokinetics of dihydrogen, with even fewer focusing on the inhalational route of administration. Liu and co-workers [10] were among the first to assess the pharmacokinetics of inhalational hydrogen, reporting that inhalation of up to 4% dihydrogen in a rat model resulted in a gradual increase in blood and tissue hydrogen levels, stabilizing after approximately 30 minutes. The extent of this increase was shown to depend on the dose administered. Yamamoto and co-workers [4] further explored dihydrogen pharmacokinetics by measuring its distribution in various organs following continuous inhalation of 3% hydrogen gas. Their findings revealed significant variability in saturation dynamics and distribution among target organs, with peak hydrogen levels observed in the liver and brain, both of which are characterized by high blood flow, supporting the notion of tissue-specific uptake and redistribution. Similar findings have been reported in other animal models, including pigs [5] and rodents [11,12], underscoring the importance of inhalation duration in systemic hydrogen distribution. Our study aligns with these findings while advancing this field by employing variable interventional protocols, extending monitoring durations, and providing a comprehensive evaluation of dihydrogen pharmacokinetics in healthy human participants. As anticipated, we found that hydrogen inhalation elicited a notable increase in blood hydrogen levels, with peak concentrations achieved within the first 30 minutes post-inhalation. Specifically, peak concentrations were observed immediately after the inhalation in the long-term protocol, at 15 minutes in the short-term protocol, and at 30 minutes in the medium-term protocol. As a gaseous and exceptionally small molecule, dihydrogen readily crosses the alveolar-capillary barrier through passive diffusion [13], entering the circulation in a dose-dependent manner. A dose-dependent effect of dihydrogen is likely evidenced by the significantly greater area under the concentration-time curve observed for the high-dose protocol (102.3 $\mu\text{g/L}\cdot\text{min}$), indicating enhanced systemic exposure with increased dosage. Interestingly, the maximum blood dihydrogen concentrations were comparable across the three inhalation protocols,

indicating potential saturation of absorption mechanisms or delayed absorption kinetics at higher dosages, which may limit the amount of hydrogen entering the bloodstream irrespective of the administered dose. A consistent observation across all protocols was the decline in blood hydrogen levels after reaching peak concentrations, followed by a modest rebound effect approximately 60–90 minutes post-inhalation. This rebound phenomenon likely reflects the subsequent release of hydrogen from highly perfused tissues and/or those with significant absorption capacity, suggesting a dynamic redistribution process within the body following initial systemic uptake [4]. We also observed similar values for the volume of distribution across the different inhalation protocols, likely reflecting the unrestricted diffusion of dihydrogen into tissues without dose-dependent barriers or binding limitations. By 120 minutes post-inhalation, blood hydrogen concentrations returned to levels comparable to pre-inhalation in all three protocols, suggesting the complete elimination of hydrogen from circulation, irrespective of the administered dose. This observation aligns with the comparable apparent total clearance values across the protocols, indicating that dihydrogen metabolism and elimination follow non-saturable pathways, unaffected by variations in dosage.

Our study provides preliminary evidence for estimating the degree of increase in blood dihydrogen concentration required for inhalational dihydrogen to be considered effective. Based on established pharmacokinetic principles [14,15], the minimal effective concentration (MEC)—the lowest concentration at which the drug produces a therapeutic effect—of inhalational hydrogen can be estimated to be approximately two- to five-fold higher than baseline concentrations. Considering the baseline pre-inhalation blood hydrogen levels in our trial (0.21 $\mu\text{g/L}$), the MEC for hydrogen can be estimated to range from 0.42 to 1.05 $\mu\text{g/L}$ (mean: 0.74 $\mu\text{g/L}$). It appears that all three inhalational protocols achieved concentrations above the upper limit of the estimated MEC at their maximum values. Some drugs require substantial increases in blood concentration to achieve peak effectiveness [16], particularly fast-acting drugs, which may be applicable to inhalational hydrogen. Typically, drugs must increase by 50–100% above the MEC to reach effective levels, although for some drugs, this increase can be several times higher (*e.g.*, up to five times the MEC), depending on the pharmacokinetics and the therapeutic window. Therefore, the effective concentrations for blood dihydrogen can be estimated to range from 0.63 to 5.25 $\mu\text{g/L}$. In our study, only the high-dose inhalation protocol maintained blood dihydrogen concentrations above the lower threshold of the estimated effective concentration range throughout the monitoring period. Finally, drugs typically have a therapeutic window, defined by the MEC and the minimum toxic concentration (MTC). The MTC may be 20 to 50 times higher than the MEC, particularly for drugs with a wide therapeutic window. Based on this, the MTC for

inhalational hydrogen could range from 8.4 to 62.5 $\mu\text{g/L}$; however, none of the inhalational protocols in our study reached these levels. Above ranges are preliminary and highly dependent on the specific therapeutic profile of inhalational dihydrogen, which warrants further investigation. Currently, no established dose-response standards exist for the use of dihydrogen in human medicine. The only guideline available is proposed by the International Hydrogen Standards Association (www.intlhsa.org) for oral hydrogen, which suggests a minimum daily intake of 0.5 mg of hydrogen in oral solutions to elicit a biological effect. However, this recommendation lacks comprehensive evidence regarding the appropriate dosage of dihydrogen, its biodynamics following intake, and the specific biological effects it may induce. Our study offers preliminary data and potential ranges for the minimum effective dose and concentration of inhaled dihydrogen, contributing to a deeper understanding of the complex kinetics of this experimental medical gas.

Despite providing valuable insights into the pharmacokinetics of inhalational dihydrogen in healthy humans, this study has several limitations. First, the small sample size limits the generalizability of our findings, and future studies with larger, more diverse participant groups are needed to confirm the results and account for inter-individual variability. Additionally, the study included only healthy male participants, which limits the generalizability of the findings to females and to individuals with various health conditions who may respond differently to the intervention. While the study assessed blood hydrogen concentrations at multiple time points post-inhalation, the long-term effects of repeated inhalation and the potential for accumulation of hydrogen over time were not explored. Furthermore, the use of a single method to measure blood hydrogen concentration, although highly sensitive, may not capture all potential variations in hydrogen dynamics within different tissue compartments. In this study, we utilized non-compartmental analysis, which assumes linear kinetics for dihydrogen. However, dihydrogen may exhibit non-linear pharmacokinetics, and the non-compartmental approach does not account for the detailed distribution of dihydrogen across tissues or organs, nor does it provide mechanistic insights into its behavior, such as the identification of rate-limiting steps in absorption or elimination. To overcome these limitations, future studies with inhalational hydrogen could benefit from employing compartmental or physiologically based pharmacokinetic models. Lastly, while the study focused on the pharmacokinetics of dihydrogen in healthy individuals, the effects of inhalational hydrogen in individuals with respiratory, cardiac, renal, hepatic, or metabolic diseases, remain unclear and warrant further investigation. Future studies should aim to address these gaps, explore the pharmacokinetics in broader populations, and assess the therapeutic potential of inhalational hydrogen in diverse clinical settings.

5. Conclusions

This pilot study provides valuable insights into the pharmacokinetics of inhalational hydrogen in healthy humans. Our findings demonstrate that inhalation duration plays a critical role in hydrogen absorption and systemic distribution, with the 45-minute protocol yielding the highest blood hydrogen concentrations and greatest systemic exposure. These results underscore the dose-dependent nature of hydrogen pharmacokinetics and suggest that prolonged exposure may be more effective in achieving therapeutic concentrations. While the study indicates that inhalational hydrogen reaches concentrations sufficient to potentially exert therapeutic effects, further research is needed to establish precise therapeutic windows and optimize dosing protocols for various medical applications. Given the promising results and the lack of significant adverse effects, inhalational hydrogen shows potential as a viable therapeutic tool, warranting additional clinical trials to fully elucidate its benefits and mechanisms in human health.

Statements

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Statement of Ethics

Study approval statement: The ethical approval was granted by the local IRB (# 9-09-14/2023-2).

Consent to participate statement: Written informed consent was obtained from all respondents to participate in the study. The research was conducted ethically following the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

All authors declare no competing interests.

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None.

Author Contributions

Conceptualization: SMO, NT, DN, MV; Methodology: all authors; Formal analysis: SMO, NT, JP, TTB; Supervision: SMO, MV; Writing - original draft: SMO, NT; editing: all authors.

Data Availability Statement

All data analyzed are included in the article. Further

inquiries can be directed to the corresponding author.

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