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REVIEW ARTICLE

Molecular hydrogen: An inert gas turns clinically effective

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Molecular hydrogen (H_2) appeared as an experimental agent in biomedicine approximately 40 years ago, yet the past 5 years seem to confirm its medicinal value in the clinical environment. H_2 improves clinical end-points and surrogate markers in several clinical trials, from metabolic diseases to chronic systemic inflammatory disorders to cancer. However, less information is available concerning its medicinal properties, such as dosage and administration, or adverse reactions and use in specific populations. The present paper overviews the clinical relevance of molecular hydrogen, and summarizes data from clinical trials on this innovative medical agent. Clinical profiles of H_2 provide evidence-based direction for practical application and future research on molecular hydrogen for the wider health care community.

Key words: Antioxidant, clinical trials, cholesterol, inflammation, molecular hydrogen

Key messages

- Molecular hydrogen (H_2) emerges as a novel medical gas within the clinical environment.
- Oral hydrogen alleviates lipid metabolism disorder in metabolic syndrome and diabetes, and ameliorates acute and chronic inflammation biomarkers in clinical trials.
- H_2 improves patient-reported outcomes in Parkinson's disease, rheumatoid arthritis, and patients with liver tumors; however, limited data are available concerning H_2 toxicity, pharmacokinetic information, and pharmacodynamics.

Introduction

In October 1975, an expert group from Baylor University and Texas A&M University reported newly identified therapeutic effects of gaseous hydrogen (molecular hydrogen, H_2), formerly considered as a biologically inert gas with low capacity to react with most biomolecules (1). Using hyperbaric mixture of oxygen (2.5%) and molecular hydrogen (97.5%), the authors reported a marked regression of squamous cell carcinoma in mice, suggesting that H_2 therapy might also prove to be of significance in the treatment of different medical conditions. The following decades documented beneficial effects of supplemental H_2 in a plethora of experimental disease models (for review see 2–4). The seminal paper describing the therapeutic effect of hydrogen as a novel antioxidant gas that selectively reduces cytotoxic oxygen species in cultured cells was published by Ohta's group in 2007 (5). Since then, more than 250 peer-reviewed articles have appeared in leading biomedical journals describing the biological effects of H_2. Inhaling hydrogen gas has been shown to be effective with rat models of acute inflammatory and oxidative diseases, including brain and myocardial infarction (6) and post-cardiac arrest syndrome (7). Hydrogen gas also neutralized oxygen toxicity in a rat model of hyperoxic lung injury (8). In addition to animal studies, the past 5 years seem to confirm the medicinal value of H_2 in the clinical environment. Delivered either via a topical, parenteral, or enteral route, H_2 improved clinical end-points and surrogate markers in several clinical trials, from metabolic diseases to chronic systemic inflammatory disorders. Now recognized as a cellular mediator in a wide range of biological activities (2–5), molecular hydrogen emerges as another member of the medical gases family that might have an important role in clinical medicine.

Clinical relevance of molecular hydrogen

The molecular hydrogen epoch in clinical medicine started in 2008, when Kajiyama and co-workers reported beneficial effects of hydrogen-rich water in patients with type 2 diabetes (9). Since then, the therapeutic effects of molecular hydrogen have been evaluated in patients with cancer, neurovascular, metabolic, and inflammatory diseases, and traumatic injuries (Figure 1).

The rationale for H_2 use in clinical medicine is mostly due to its antioxidant properties. Since oxidative stress plays a major role in many pathologies (25), one would expect that molecular hydrogen as a selective antioxidant might positively affect oxidative stress-related disorders, such as neurodegenerative diseases or atherosclerosis. Indirect evidence via monitoring biomarkers such as reactive oxygen species production and antioxidant defense outcomes suggested that H_2 diminished oxidative stress in patients with diabetes mellitus (9), potential metabolic syndrome (10), hemodialysis and peritoneal dialysis (11,20), cancer

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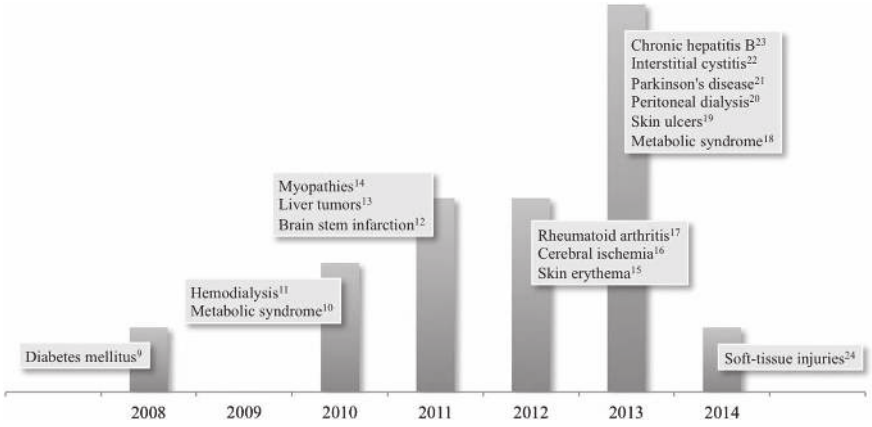

Figure 1. Timeline for clinical trials with molecular hydrogen.

patients receiving radiotherapy (10), patients with mitochondrial and inflammatory myopathies (14), rheumatoid arthritis (17), and chronic hepatitis B (23). However, less information is available concerning the therapeutic effects of molecular hydrogen on clinically meaningful end-points, such as relevant laboratory measurements, or patient-reported outcome measures.

Several small clinical trials analyzed the lipid-lowering effects of molecular hydrogen. A randomized, double-blind, placebo-controlled, cross-over trial of 900 mL/day of hydrogen-rich water for 8 weeks in 30 patients with diabetes mellitus type 2 demonstrated a significant decrease of low-density lipoprotein (LDL)-cholesterol and small dense LDL by 15.5% and 5.7%, respectively (9). An open-label trial of 1.5–2.0 L/day of hydrogen-rich water in 20 patients with metabolic syndrome reported an 8% increase in high density lipoprotein (HDL)-cholesterol, and a 13% decrease in total cholesterol/HDL-cholesterol (10). In addition, serum total cholesterol and LDL-cholesterol were decreased by 14.8% and 18.2%, respectively, after 10 weeks of treatment with 0.9–1.1 L/day of hydrogen-rich water in 20 patients with potential metabolic syndrome (18). Although the studies were small in size and of short duration, it appears that H_2 can alleviate lipid metabolism disorder, including hyperlipidemia and defective HDL, in metabolic syndrome and diabetes. Possible mechanisms by which H_2 regulates lipoprotein profiles include improved insulin sensitivity (9), inhibition of cholesterol synthesis in the liver (18), and up-regulation of the gene expression of the hepatic hormone, fibroblast growth factor 21 (26).

Molecular hydrogen affected acute and chronic inflammation biomarkers in several clinical trials. Adding H_2 to hemodialysis (HD) solution ameliorated inflammatory stress, as assessed via a drop in plasma monocyte chemoattractant protein-1 of 9.6% and myeloperoxidase of 8.2%, in 21 renal disease patients who were switched from standard HD solution to hydrogen-rich HD during 6 months (11). An open-label trial of 1.0 L/day of hydrogen-rich water for 12 weeks in four patients with polymyositis and/or dermatomyositis showed a significant drop in serum matrix metalloproteinase-3, an enzyme that facilitates lymphocyte adhesion and enhances T cell-mediated cytotoxicity, of 7.8% (14). As an additional agent to supplement traditional conservative treatment of acute injury, 2-week administration of oral hydrogen (2 g per day) and topical hydrogen-rich packs (6 times per day for 20 minutes) significantly reduced plasma viscosity, a non-specific *marker of acute inflammation*, by 16.5% in 36 male professional athletes after acute soft tissue injury (24). On the other hand, intake of 530 mL/day of hydrogen-rich water for 4 weeks in 20 patients with rheumatoid arthritis (RA) revealed no significant effects on serum anti-cyclic citrullinated peptide antibodies, a sensitive inflammatory marker for diagnosis and prognosis in RA (17). These conflicting results could be due to simple difference in dose of H_2 administered, or a complex role H_2 might play in inflammation. Although oxidative stress is involved in the development of inflammation (27), the antioxidant effect of hydrogen may not be the only driving factor causing the anti-inflammatory effects of administration in the above trials; the possible impact of H_2 on down-regulation of proinflammatory cytokines might be involved (2).

There is growing evidence that H_2 can improve patient-reported outcomes. Yoritaka and colleagues recently reported data on the efficacy of 48-week H_2 therapy in 18 patients with levodopa-medicated Parkinson's disease (PD) in symptom-oriented randomized controlled trial (RCT) (21). The authors reported an improvement in total unified PD rating scale score (UPDRS; score ranges from 0 to 199, with higher scores indicating greater disability) of approximately –5.7 units (95% CI –12.2, 0.8) in patients that received 1.0 L/day of molecular hydrogen. Another symptom-centered study investigated the effects of 6-week hydrogen therapy (hydrogen-rich water, 1.5–2.2 L/day) in 49 patients treated with radiotherapy for liver tumors (13). Data showed that hydrogen administration prevented a radiotherapy-induced drop in the quality of life scores (QLQ-C30; score ranges from 0 to 9, with higher scores reflecting decreased quality of life) of approximately 4.0 units as compared to the placebo at post-administration. In addition, fewer appetite loss episodes and fewer tasting disorders were reported in patients treated with H_2. Hydrogen improved symptoms of rheumatoid arthritis (RA) when administered for 4 weeks in a Japanese RCT (17). Disease activity score in 28 joints (DAS28; score ranges from 0 to 10, with higher scores indicated higher RA activity) decreased by 21.2% during the intervention, suggesting that H_2 could complement conventional therapy in RA. Also, H_2 intervention resulted in a faster return to normal joint range of motion of the injured limb as compared with the control intervention in professional athletes after acute soft-tissue injury (24). In a clinical trial conducted in Japan, 600 mL/day of hydrogen-rich water administered via tube feeding improved healing in 22 patients with pressure ulcers (19). Wound size decreased by approximately 6 cm^2 after H_2 intervention, with a reduction in hospitalized days for patients treated with hydrogen versus the control group (113.3 days versus 155.4 days). On the other hand, Ito and co-workers observed no improvement or worsening of clinical symptoms after 12-week open-label study and randomized double-blind, placebo-controlled cross-over trial of 1.0 L/day of hydrogen-enriched

water in 36 patients with mitochondrial and inflammatory myopathies (14). In a similar double-blind placebo-controlled, randomized trial, 30 patients with interstitial cystitis/painful bladder syndrome (IC/PBS) that received 600 mL/day of hydrogen-rich water for 8 weeks demonstrated no differences in reduction of relevant symptoms (e.g. pelvic pain, bladder pain score, voiding frequency) as compared to the placebo (22). It seems that hydrogen might positively affect clinical symptoms in several pathologies, yet the results should be interpreted with caution due to limitations in trial design and small sample sizes; the results of clinical trials do not support the use of H_2 for treating patients with myopathies or IC/PBS.

New frontiers for molecular hydrogen

Molecular hydrogen has already entered a therapeutic arena; however, several enigmas are yet to be resolved before its recognition as a safe and efficient medical agent. So far, limited data are available concerning H_2 toxicity, pharmacokinetic information, and pharmacodynamics. Dose escalation studies are absent at the moment, and the optimal and safest dose range for H_2 remains unknown. Another concern regarding its administration is the variation in the H_2 content across suppliers and various formulations (28). Molecular hydrogen is generally considered to be a safe agent, with most clinical trials revealing no adverse events or mild side effects (e.g. minimal disturbances in liver enzymes, gastrointestinal distress) after H_2 administration (29). The safety of gaseous H_2 is demonstrated by its application in breathing gas mixture of 49% H_2, 50% helium, and 1% oxygen, which is used to prevent decompression sickness and nitrogen narcosis during very deep technical diving (30,31). However, no clinical trials focused on the safety of H_2 application have been conducted to date. In addition, previous clinical studies with H_2 were mostly non-randomized and open-label trials, with small sample sizes (e.g. $\leq$60 participants) and short durations (e.g. $\leq$48 weeks). Appropriately designed, long-term, large-scale, prospective clinical trials are warranted to examine further the therapeutic potential of H_2 in different pathologies. A brief summary of medicinal information for molecular hydrogen collected from clinical trials is presented in Table I.

Molecular hydrogen has several possible advantages as an innovative therapeutic agent in clinical medicine. The small molecular size enables its rapid diffusion to target tissues and cells (3), while physiological variables (e.g. pH, oxygen saturation, temperature, blood pressure) are not affected by molecular hydrogen administration (10,15,16,20). In addition, molecular hydrogen could be delivered via different routes of administration, including inhalation, oral route, hemodialysis and intraperitoneal

Table I. Brief summary of medicinal information for H_2 collected from clinical trials.

Medicinal information on H_2 collected from clinical trials			References
Indications and usage	Not clear; for treatment of oxidative stress-related diseases/disorders.		9–24
Dosage and administration	*Oral formulations:*		9, 10, 13, 14, 17–19,
	Water solution: $[H_2] = 0.25–0.80$ mmol/L	100–400 mL three to ten times a day	21–23
	Tablet: $[H_2] = ?$	(total maximum consumption per day = 2000 mL)	24
		700 mg three times a day	
	Hemodialysis solution: $[H_2] = 24$ µmol/L	500 mL/min flow, three sessions per week	11, 20
	Intravenous solution: $[H_2] = 0.25–0.80$ mmol/L	250–500 mL twice daily	12, 15
	Gas mixture: $[H_2] = 2\%–4\%$	20 min once daily	16
	Topical gel: $[H_2] = ?$	125 mL six times per day for 20 minutes	24
Contraindications	There have been no clinical studies establishing conclusive evidence of contraindications with H_2. Hypersensitivity to H_2 products?		
Warnings and precautions	Hydrogen gas poses risk of explosion in air and in pure oxygen when present at concentrations >4%; desired concentration of H_2 must be monitored and maintained with an appropriate device.		2
Adverse reactions	Adverse reactions reported by 2% or more of adult patients taking hydrogen-rich oral formulations in clinical trials: loose stools (15%); floating sensation (7%); increase in frequency of bowel movement (5%); heartburn (5%); headache (5%).		10, 11, 14, 21, 22, 24
Drug interactions	No evidence; however, this does not necessarily mean no interactions exist.		
Use in specific populations	*Pregnancy:* There are no adequate and well-controlled studies with H_2 in pregnant women. *Nursing mothers:* No information is available on whether H_2 is excreted in breast milk. *Pediatric use:* Safety and effectiveness of H_2 in patients <18 years of age have not been established. *Geriatric use:* Of the total numbers of subjects in the clinical trials ($n = 419$), H_2 was administered to 79 patients aged 65 and older. Of those, 29 patients were 75 years and older. No study compared incidence of hydrogen-related adverse events among subjects >65 years of age and young adults. No pharmacokinetics were established in the healthy elderly and elderly subjects taking H_2. *Renal impairment:* The efficacy and safety of H_2 hemodialysis solution were evaluated in a study that included 21 patients with severe renal impairment (no eGFR data were available) receiving dialysis; patients treated with H_2 were more likely to experience increases in BUN and creatinine. *Hepatic impairment:* In a study utilizing oral hydrogen, liver function (ALT, TbiL, ChE) in 60 patients with moderate hepatic impairment due to chronic hepatitis C did not change as compared to those observed in subjects with normal hepatic function. *Gender:* Dosage adjustment of H_2 on the basis of gender has not been evaluated.		11, 20, 23
Drug abuse and dependence	No clinical studies evaluated H_2 abuse and/or dependence.		
Overdosage	There were no reports of overdose during the clinical trials of H_2; however, this does not necessarily mean no overdose exists.		
Patient counseling information	No organization or industry provides patient counseling information for H_2 according to FDA guidelines.		

ALT = alanine aminotransferase; BUN = blood urea nitrogen; ChE = cholinesterase; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; TbiL = total biliary acid.

dialysis, intravenous infusion, and epicutaneous administration. Multiple routes of administration along with low cost per treatment (2) make molecular hydrogen a convenient agent for extensive clinical use, if evidenced for safety and efficacy. One of the most promising areas of research with molecular hydrogen involves gas inhalation in acute circulatory disorders, with the potential dramatically to improve treatment of brain, kidney, or myocardial ischemia-reperfusion injury, as already demonstrated in animal studies (6,7). Upcoming human trials with H_2 should primarily evaluate its effectiveness in these acute clinical settings.

The fate of molecular hydrogen in biomedicine appears to be similar to other members of the medical gases family (such as NO, H_2S, and CO) that were all initially regarded as irrelevant factors. Ten years ago we considered molecular hydrogen as an inert gas; today we see it as a therapeutic agent with very wide application options in clinical medicine. Although the current published data on molecular hydrogen are sparse, the favorable effects of H_2 therapy demonstrated in the majority of preliminary trials encourage future research; understanding its actions might lead us to new forms of H_2 therapy for human disease.

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Declaration of interest: The author declares no competing interests.

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