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CASE REPORT

Severe hypomagnesaemia in the intensive care unit

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Abstract

This report describes a patient admitted to the intensive care unit (ICU) with extreme hypomagnesaemia (0.03 mmol/l). Profound weakness and rhythm disturbances were the most pronounced symptoms. This patient exhibited six risk factors for hypomagnesaemia: chronic dysphagia, acute diarrhoea and vomiting, high alcohol intake, use of a proton pump inhibitor and a diuretic. Despite this extreme hypomagnesaemia, he survived hospital admission.

In order to determine the incidence of severe hypomagnesaemia (< 0.40 mmol/l) and its risk factors and manifestations, we searched our ICU patient database which included 21,296 patients. The incidence of severe hypomagnesaemia on ICU admission was 0.24%. Patients with severe hypomagnesaemia had a 44% incidence of sepsis and arrhythmia; 23% presented with a recent history of alcohol abuse, 36.5% had used a proton pomp inhibitor, half had acidosis and hyponatraemia, and 97% had low ionised calcium. Mortality lower than predicted.

Although the literature reports that hypomagnesaemia occurs in up to 60% of ICU patients, severe hypomagnesaemia (< 0.40 mmol/l) was rare in the present population. Despite the seemingly crucial metabolic role of magnesium, severe hypomagnesaemia was not significantly associated with mortality in our unit.

Introduction

Hypomagnesaemia is reported in 20-65% of critically ill patients[1,2] and its occurrence has been associated with mortality.[3,4] This report describes a patient who presented with a serum magnesium level of 0.03 mmol/l on ICU admission. In order to determine the incidence of severe hypomagnesaemia and its risk factors and manifestations, we searched our ICU patient data management system for patients admitted with severe hypomagnesaemia, which we arbitrarily defined as a plasma concentration of < 0.40 mmol/l. In addition, we have summarised the pathophysiology, risk factors and clinical consequences of hypomagnesaemia and possible therapeutic benefits of magnesium in critically ill patients.

Case report

A 70-year-old male was admitted to the internal medical ward with diarrhoea and acute kidney injury, severe malnutrition and acute confusion. His medical history included hypertension, pulmonary embolism, chronic renal disease, villous polyps of the colon and alcohol abuse. Four years previously, he had received radiation therapy for a malignant neoplasm of the glottis, which had resulted in dysphagia and intermittent aspiration. He resided in a nursing home; he was reasonably independent regarding daily activities, but not for personal care. His daily medications included amlodipine, lisinopril, metoprolol, hydrochlorothiazide, pantoprazole, thiamine and alfacalcidol.

The patient was urgently admitted to the ICU because of acute respiratory insufficiency presumably due to aspiration. A physical examination showed a severely dyspnoeic, extremely weak and exhausted patient with a respiratory rate of 48/min and an oxygen saturation of 90% with 20 litres of oxygen by mask. Breathing sounds over the right lower lobe were diminished and his extremities were cold. He had on-and-off supraventricular tachycardia and atrial fibrillation at a frequency of 200 bpm with multiple premature ventricular contractions and his arterial blood pressure was 129/76 mmHg. At the time of the electrocardiogram, he had a supraventricular tachycardia of 191 beats/min, low voltage, QRS 82 ms, QTc 460 ms, ST elevation in leads I and aVL, ST depression in III, aVF, V5-6 and peaking of T waves. The patient was immediately

intubated and mechanically ventilated, and purulent secretions were suctioned from the tube. Atrial fibrillation was initially treated with one dose of metoprolol 5 mg and magnesium intravenously, followed by amiodarone as a continuous infusion. The ST-T segments normalised and cardiac enzymes remained negative. We administered cefotaxim and ciprofloxacin for suspected aspiration pneumonitis, thiamine and initiated enteral nutrition. Because the sputum culture demonstrated no pathogenic microorganisms, antibiotics were discontinued after three days. Additional treatment during admission consisted of intravenous rehydration and haloperidol for delirium. Laboratory results from blood taken on admission are presented in *table 1*. An extremely low concentration of magnesium (0.03 mmol/l) was detected and confirmed in duplicate. During the first 12 hours of ICU treatment, a total of 50 mmol of intravenous magnesium sulphate was administrated in slow intermittent boluses. The serum magnesium concentration recovered. Initial haloperidol treatment for delirium was discontinued because the patient developed a long QTc interval. The patient quickly recovered and after three days he was discharged to the internal medical ward with normal sinus rhythm, without confusion, and with a plasma magnesium concentration of 0.91 mmol/l.

A detailed examination for tremor and nystagmus was unfortunately not performed due to the need for emergency intubation. In addition, blood for parathyroid hormone, vitamin D, thiamine and urine for magnesium excretion were not taken.

Database search

This case prompted us to study the incidence of severe hypomagnesaemia upon ICU admission and specifically how often these patients used a proton pump inhibitor (PPI), a known risk factor for hypomagnesaemia. We therefore searched the ICU patient data management system (MetaVision®, iMDsoft, Tel Aviv, Israel). The unit is a mixed surgical-medical ICU of a teaching hospital in Amsterdam with the largest emergency department in the city. Except for neurosurgery, all medical specialities are present in the hospital including cardiac surgery. We extracted all patients who had severe hypomagnesaemia on ICU admission. Severe hypomagnesaemia was arbitrarily defined as serum concentration of < 0.40 mmol/l. We additionally extracted demographic variables, age, gender, reason for ICU admission, risk factors for hypomagnesaemia (especially the use of a PPI), and clinical symptoms. The severity of the disease was calculated on the day of admission to the ICU using the Acute Physiological and Chronic Health Evaluation (APACHE) II scoring system.[1]

From January 2000 to July 2012, a total of 21,296 patients were admitted to our ICU. Mean magnesium concentration on admission was 0.86 ± 0.24 mmol/l (results were available in 20,963 patients, 98.4%). A serum magnesium concentration of < 0.40 mmol/l on ICU admission was found in 52 (0.24%) of all ICU admissions and in 0.25% of all admissions with available magnesium. Demographic data of the patients with severe hypomagnesaemia are presented in *table 2*. The mean age of the severely hypomagnesaemic patients was 60 ± 13.6 years; 21

Table 1. Main laboratory results of the patient with extreme hypomagnesaemia at ICU admission

pH	7.26	
pCO2	43	mmHg
PO2	62	mmHg
Bicarbonate	18.7	mmol/l
Base excess	7.6	mmo/l
SaO2	86	%
Lactate	2.5	mmol/l
Sodium	144	mmol/l
Potassium	3.0	mmol/l
Total calcium	1.64	mmol/l
Ionised calcium	0.89	mmol/l
Magnesium	0.03	mmol/l
Albumin	35	g/l
Phosphorus	1.18	mmol/l
Creatinine	86	µmol/l
Urea	21.3	mmol/l
Alkaline phosphatase	39	IU/l
γGt	23	IU/l
C-reactive protein	46	mg/l
ASAT	64	IU/l
ALAT	29	IU/l
Glucose	9.2	mmol/l

Table 2. Clinical characteristics and mortality of the patients with severe hypomagnesaemia

	N = 52
Gender	
- Male	21 (40)
- Female	31 (60)
Age	60 ± 13.5
Type of admission	
- Surgical[a]	28 (54)
- Non-surgical	24 (46
APACHE II	20.7 ± 7.1
APACHE II predicted mortality	0.38 (95% CI 0.26-0.53)[b]
Standardised mortality (SMR)	0.39 (95% CI 0.16-0.83)[b]
Sepsis	23 (44)b
Arrhythmias	23 (44)
Bleeding	9 (17)
Use of PPI	19 (37)
Alcohol abuse	12 (23)
Magnesium concentration (mmol/l)	0.33 ± 0.07
Hospital mortality	8/52 (15.4 %)

Results in number (%), mean ± SD. or mean (95% confidence interval (CI))
[a]Surgery within one week prior to ICU admission, [b]APACHE II and SMR predicted mortality could only be calculated for 47 patients, not for the other 5 patients due to ICU admission < 24 hours

(40.4%) were females, 28 (53.8%) were admitted after surgery, 7 after elective, 7 after scheduled and 14 after urgent surgery. Nine patients (17.3%) had bleeding complications before admission, 23 (44.2%) had sepsis and 23 had dysrhythmia. Nineteen (36.5%) had a history of PPI use. The mean APACHE II score was 20.7 (SD 7.1) and hospital mortality was 15.4%, lower than predicted by the APACHE II system (standardised mortality ratio 0.39, 95% CI 0.26-0.81). In *table 3*, plasma concentrations of magnesium, calcium, phosphate, creatinine and acid base of the patients with severe hypomagnesaemia are presented. Hypocalcaemia was present in 97% of the patients. However, albumin was low (22 ± 7 g/l) and corrected hypocalcaemia was only present in 35%. Ionised hypocalcaemia was found in 97%. The incidence of metabolic acidosis was over 50%.

Discussion

Hypomagnesaemia, as defined by a total plasma concentration less than 0.7 mmol/l, is an underdiagnosed but common electrolyte abnormality in critically ill patients. Estimates of magnesium deficiency range from 20-61%.[2] Our patient was admitted to the ICU with an extremely low serum magnesium concentration, 0.03 mmol/l, and he nevertheless survived. He presented with cardiac arrhythmias, delirium, apathy, extreme weakness and electrolyte disturbances. A detailed neurological examination could not be performed because of the severe exhaustion necessitating acute intubation. Our patient exhibited several risk factors. First, he suffered from dysphagia after radiotherapy for glottis carcinoma resulting in a poor nutritional status. Second, his alcohol intake was high. Third, he had a period of severe diarrhoea and vomiting of unknown cause, but the gastrointestinal symptoms disappeared during hospital admission. Fourth, he additionally used a PPI and a thiazide diuretic. The combination of these risk factors had likely contributed to the extreme hypomagnesaemia.

In our ICU cohort, severe hypomagnesaemia (< 0.40 mmol/) was rare, it was observed in only 0.24%. Of them 44% presented with sepsis. 44% exhibited cardiac dysrhythmias, 37% used a PPI and 23% abused alcohol. Unfortunately, we have no exact data on the last three above mentioned risk factors in the overall ICU population. In addition, 17% of the patients were admitted after bleeding. This relation may be explained by the loss of magnesium without replacement. Mortality was lower than predicted.

Table 3. Biochemical data of the severely hypomagesaemic patients

	Mean ± SD mmol/l	Low n (%)	Normal n (%)	High n (%)
Potassium (mmol/l)	3.9 ± 0.7	16 (30)	31 (60)	5 (10)
Sodium (mmol/l)	136 ± 4.8	28 (54)	23 (44)	1 (2)
Total calcium[b] (mmol/l)	1.8 ± 0.26	36 (92)	3 (8)	0 (0)
Ionised calcium[c] (mmol/l)	1.0 ± 0.2	39 (97)	1 (3)	0 (0)
Phosphate (mmol/l)	1.1 ± 0.39	13 (25)	27 (52)	12 (23)
pH	7.19 ± 0.10	29 (56)	20 (38)	3 (6)
Bicarbonate (mmol/l)	18.5 ± (4.7)	37 (71)	13 (25)	2 (4)
Base excess	6.2 (5.3)	40 (77)	11 (21)	1 (2)
Creatinine (µmol/l)	115 ± 129	3 (6)	23 (44)	26 (50)

Results in mean ± SD or n (%) , [b] in 13 patients the concentration of calcium at ICU admission was not available [c] in 14 patients the concentration of ionised calcium at ICU admission was not available
Normal range: potassium: 3.6-5.2 mmol/l, sodium 137-147 mmol/l, total calcium 2.15- 2.6 mmol/l, ionised calcium 1.19- 1.31 mmol/l, phosphate 0.85- 1.4 mmol/l, pH 7.35-7.45, bicarbonate 22-26 mmol/l, base excess -2 - +2, creatinine 45-90 µmol/l (women) and 60-110 (men)

Physiology of magnesium homeostasis

Magnesium is the fourth most abundant cation in the human body and after potassium the second most abundant intracellular cation. Magnesium plays a role as a cofactor in more than 300 enzymatic reactions involving control of calcium and potassium channels, membrane stabilisation, neuromuscular excitability, protein and nucleic acid synthesis and oxidative phosphorylation.[2]

The total body magnesium content of a normal adult is approximately 25 g, of which 53% is found in bone, 27% in muscle, 19% in soft tissues, 0.5% in erythrocytes and 0.5% in serum. Sixty-seven percent of all plasma magnesium circulates in an ionised form; 19% is protein bound and 14% circulates complexed to fatty acids and anions such as phosphate, citrate or bicarbonate.[2,3] Within the cell, magnesium is mostly chelated to adenosine triphosphate (ATP), adenosine diphosphate (ADP), proteins, RNA, DNA, and citrate. Although the ionised serum magnesium fraction is small, this fraction regulates homeostasis. The plasma magnesium concentration is determined by gastrointestinal absorption and renal excretion, but is also regulated by exchange with bone and partially by parathyroid hormone (*figure 1*).

Intestinal magnesium absorption occurs by passive paracellular movement through the tight junctions between the enterocytes. Active transport in the gut goes through the transient receptor potential melastatin-6 and -7 (TRPM6/7) channels, which are present in the apical membrane. The kidney is the prime organ for the fine regulation of serum magnesium. Magnesium is completely filtered by the glomerulus and is then passively reabsorbed in the proximal tubules and thick ascending loop of Henle. Active reabsorption occurs in the distal convoluted tubule through TRPM6 channels. Magnesium deficiency increases the expression of TRPM6/7 channels in the gut and TRPM6 in the kidney.[4]

The concentration of total magnesium in serum is the only readily available assessment of magnesium status in clinical practice; however, it does not adequately reflect body magnesium stores. Normal serum magnesium concentrations may be present despite intracellular magnesium depletion.

The magnesium tolerance test can detect magnesium depletion but is only reliable if renal function is normal. The test measures urinary magnesium excretion before and after intravenous magnesium loading. Retention of more than 20% of administered magnesium suggests magnesium depletion.[5] Currently, ionised magnesium is available in some blood gas analysers.

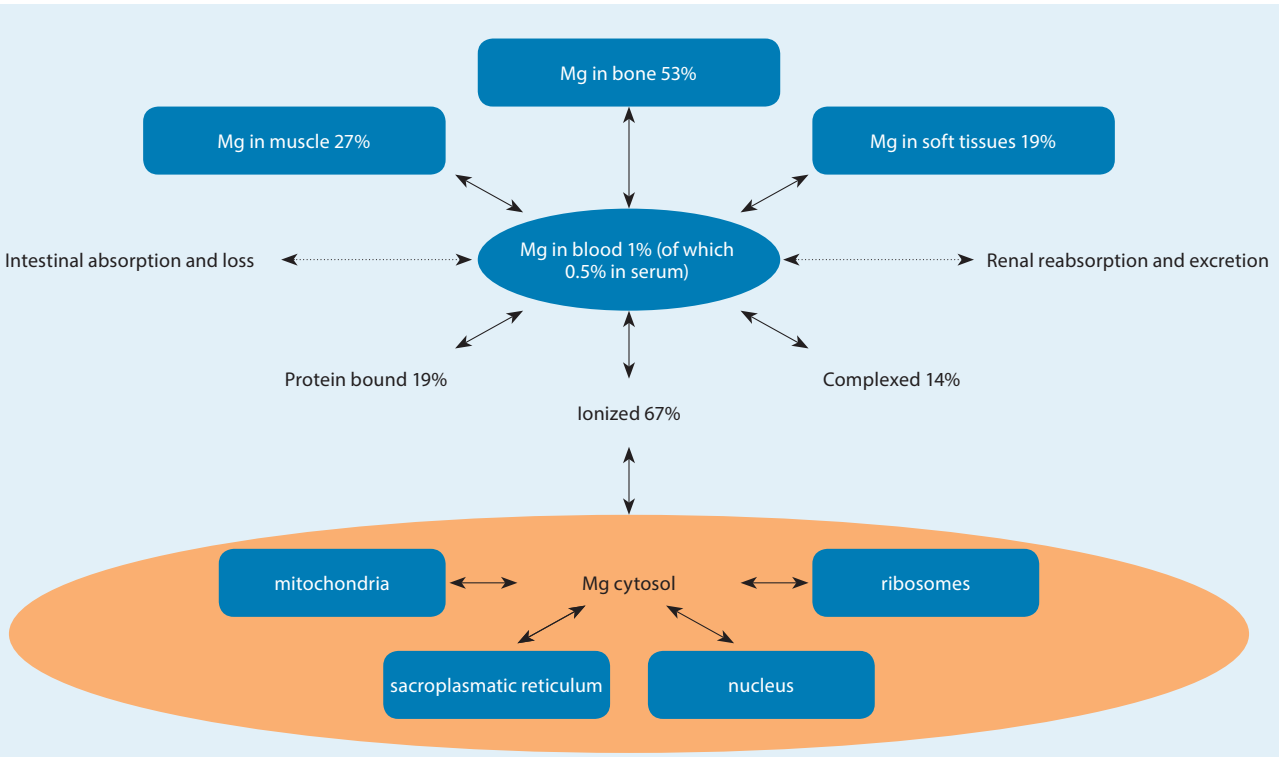
Risk factors and pathophysiology

Risk factors of hypomagnesaemia include diminished intake or absorption, increased gastrointestinal or urinary loss, or redistribution of magnesium from extracellular to intracellular sites. Low total magnesium concentration may also be due to a low plasma protein content. Hypomagnesaemia is reported in one-third of patients with chronic liver disease and alcoholism.[6] Pathogenetic mechanisms include malnutrition, malabsorption, diarrhoea and inappropriate magnesuria, possibly due to hypophosphatemia, metabolic acidosis, or a direct magnesuric effect of alcohol. Increased magnesium entry into cells can play a role in alcoholic patients due to a shift of magnesium in respiratory alkalosis or to excessive catecholamine release in alcohol withdrawal syndrome.[7] Other risk factors include poor nutrition, renal tubular dysfunction, use of diuretics, acute pancreatitis and diarrhoea, sepsis, critical illness and use of catecholamines.[2,8] Drugs such as loop and thiazide diuretics, aminoglycosides, amphotericin, cisplatin, cyclosporine, pentamidine and foscarnet are frequently associated with renal magnesium wasting.[9-11]

Relation with use of proton pump inhibitors

In addition, hypomagnesaemia has been described with all the PPIs that are substituted pyridylmethylsulphonyl benzimidazole derivatives; however, its occurrence is rare.[12-14] PPIs promote hypomagnesaemia through loss of active magnesium absorption via TRPM6/7 channels while passive paracellular magnesium absorption is intact.[4] Alternatively, susceptibility to reduced absorption could be attributed to TRPM6 mutations. Hypomagnesaemia due to PPIs does not resolve with oral supplementation, but recovers rapidly after withdrawal of the PPIs. In a large, cohort study, hypomagnesaemia associated with PPI use was restricted to patients taking diuretics.[12] Our patient used diuretics as well. PPI-associated hypomagnesaemia can occur even in advanced chronic renal failure, which is usually characterised by hypermagnesaemia.[15]

Figure 1. Magnesium homeostasis



The figure presents the magnesium distribution in the body, the percentages in the different compartments and the intestinal uptake and renal reabsorption and excretion. Protein bound – complexed – and ionised percentages reflect the respective percentages of the serum concentrations

Relation with other electrolyte disturbances

Hypomagnesaemia is often accompanied by a deficiency of other minerals. In our cohort, hypocalcaemia was observed in 92%. However this proportion decreased to 35% when corrected for low albumin. Interestingly, the proportion of ionised hypocalcaemia was 97%, which is notable because more than half of our patients had metabolic acidosis. Hypocalcaemia develops with prolonged, severe hypomagnesaemia due to the inhibition of parathyroid hormone (PTH) secretion, bone resistance to PTH and to vitamin D deficiency. Hypomagnesaemia inhibits the synthesis of 1,25-dihydroxyvitamin D.[16]

Hypokalaemia occurs in half of all hypomagnesaemic patients and is due to diarrhoea, renal loss, and to the magnesium dependency of Na-K-ATPase.[17] This enzyme actively pumps sodium across the plasma membrane out of the cell in exchange for potassium using the energy derived from ATP hydrolysis. As a result, hypomagnesaemia decreases intracellular potassium. In the kidney, magnesium deficiency increases distal potassium secretion by affecting the renal outer medullary potassium channel. Magnesium supplementation reduces potassium excretion.[18] In hypomagnesaemic patients, the correction of hypokalaemia requires magnesium supplementation.

Neuromuscular

Hypomagnesaemia promotes an influx of calcium into the presynaptic nerves increasing release of neurotransmitters and neuromuscular activity.[19] Neuromuscular symptoms of magnesium deficiency include weakness, muscle cramps, increased irritability of the nervous system, confusion, disorientation or depression. However, associated hypocalcaemia may contribute to these symptoms as well. Although magnesium administration has been reported to control status epilepticus, its effectiveness has not been proven.[20]

Cardiovascular

Hypomagnesaemia can cause coronary vasoconstriction and atrial, junctional or ventricular arrhythmias. Arrhythmias are aggravated by concomitant hypokalaemia.[21] Electrographic changes include prolonged PR and QT intervals, a widening QRS complex and the peaking of T waves. Magnesium is the treatment of choice in long-QT syndrome.[22]

Magnesium and metabolism

Hypomagnesaemia is associated with diabetes mellitus due to renal losses through glycosuria. There is a strong relationship between hypomagnesaemia and insulin resistance.[23] Magnesium supplementation decreases insulin requirements.[24] Because magnesium is a cofactor for transforming thiamine into the active thiamine pyrophosphate, symptoms of thiamine deficiency can be enhanced by hypomagnesaemia and magnesium should be supplemented together with thiamine when deficiency is suspected.[25]

Inflammation and oxidant stress

Magnesium seems to play an role in sepsis. Hypomagnesaemia is associated with increased release of endothelin and proinflammatory cytokines, macrophage activation, leucocyte adherence, granulocyte oxidative burst, endotoxin binding to monocytes and enhanced generation of reactive oxygen species.[2,8] In experimental studies, magnesium supplementation had anti-inflammatory, anti-oxidant and anti-thrombotic effects.[8]

Clinical manifestations of hypomagnesaemia are summarised in *table 4*.

Clinical studies

Hypomagnesaemia is an independent risk factor of atrial fibrillation after cardiovascular surgery and several studies have shown the benefits of prophylactic magnesium postoperatively.[26] In addition, intravenous magnesium after coronary bypass surgery reduced length of stay on ventilator, pain and N-terminal pro-brain natriuretic peptide.[27] Observational studies have suggested that hypomagnesaemia is associated with poor neurological outcomes after aneurysmatic subarachnoid haemorrhage.[28] A recent review showed that prophylactic supplementation of magnesium does not improve clinical outcomes or reduce cerebral infarction or vasospasm, but prevents delayed cerebral ischaemia which usually occurs between 4-10 days after aneurysmal subarachnoid haemorrhage.[29] Furthermore, prophylactic treatment with magnesium sulphate significantly reduces the rate of eclampsia in women at risk.[30] In addition, supplemental magnesium

Table 4. Clinical manifestations of hypomagnesaemia

Neuromuscular
Tremors and tetany
Paresthesias
Muscle weakness
Neurological
Nystagmus
Hyperactivity
Delirium
Seizures
Apathy
Coma
Cardiovascular
Supraventricular arrhythmias
Ventricular arrhythmias
Torsade de points
Impaired cardiac contractility
Vasoconstriction, hypertension
Metabolic disturbances
Hypokalaemia
Hypocalcaemia
Insulin resistance
Gastrointestinal
Anorexia, nausea, vomiting

reduced blood pressure in diabetic hypertensive adults with existing hypomagnesaemia[31] and improved insulin resistance.[24] Moreover, intravenous magnesium, added to β2-agonists and steroids, improved pulmonary function in patients with acute asthma.[32] Furthermore, hypomagnesaemia was independently associated with non-recovery of renal function among acute kidney injury patients in the ICU.[33] Whether magnesium supplementation lowers a pro-inflammatory or pro-oxidative state, or improves metabolism has not been shown in clinical studies yet.

Conclusion

We have presented a case of extreme hypomagnesaemia, 0.03 mmol/l, on ICU admission. The patient presented with confusion, exhaustion and rapid cardiac dysrhythmias. He exhibited several risk factors for hypomagnesaemia. Despite this extreme hypomagnesaemia, he survived his stay in hospital. Although hypomagnesaemia is a common problem, reported in up to 60% of ICU patients, severe hypomagnesaemia (< 0.40 mmol/l) was rare in our ICU population and was, in contrast to the literature, not associated with mortality. Whether alertness to its occurrence and a dedicated replacement strategy prevented the hypomagnesaemia from increasing the risk of mortality in the present cohort cannot be proven.

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