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Post-marketing surveillance of zinc acetate dihydrate for hypozincemia in Japan

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Zinc is an essential microelement, and its deficit causes various diseases and symptoms. In adults, especially in elderly individuals, zinc shortage can cause symptoms such as taste disorder, dermatitis, and susceptibility to infection. In children, zinc deficiency can lead to growth retardation. In 2017, the indication for zinc acetate dihydrate (NOBELZIN®) was expanded from Wilson's disease to include hypozincemia, leading to wider use of zinc acetate dihydrate. At five years after this broadening of use, we conducted a post-marketing study (PMS) to investigate the utilization, safety, and effectiveness of zinc acetate dihydrate. Over 52 weeks, the overall incidence of adverse drug reactions (ADRs) was 9.4% (87/928). The most common ADR was copper deficiency (2.4%), followed by nausea (1.4%). Among 928 patients, 19 (2%) developed serious ADRs. Of the patients with copper deficiency, 92% were >65 years of age, and all had comorbidities at baseline. Physicians evaluated the effectiveness of zinc acetate dihydrate using three categories: "effective", "not effective", and "indeterminate". The overall efficacy rate was 83.0%. The average serum zinc levels were elevated from 50–60 µg/dL to >90 µg/dL within 12 weeks, and were maintained up to 52 weeks after administration. Among the symptomatic sub-categories, the efficacy rate was highest in pressure ulcer (96.2%; 25/26), followed by in stomatitis (87.5%; 42/48), and taste disorder (87.4%; 181/207). Among pediatric patients with developmental symptoms, an efficacy rate of 66% was achieved. In conclusion, zinc acetate dihydrate has been safely used, and has produced beneficial effects on various diseases and symptoms.

1. Introduction

Zinc is an important essential microelement, the deficiency of which can lead to taste disorder, dermatitis, alopecia, anemia, stomatitis, disturbance in sexual function, predisposition to infection, and osteoporosis (Trumbo et al. 2001; Saper and Rash 2009). Moreover, in children, zinc deficiency can cause growth disturbances, such as short height or low weight (Willoughby and Bowen 2014).

One cause of zinc deficiency is insufficient intake—including due to poor nutrition, low zinc content in the mother's milk for infants, or sometimes vegan diet. Another cause is disturbed absorption of zinc resulting from chronic diseases, such as cirrhosis, diabetes mellitus, chronic inflammatory bowel disease, and excessive excretion with chronic kidney disease (Saper and Rash 2009, Maruyama et al. 2021; Kodama et al. 2018; Reddavide et al. 2018). Moreover, zinc deficiency can reportedly be caused by long exposure to drug with chelating effects, such as allopurinol, D-penicillamine, and imipramine (Tomita and Yoshikawa 2002; Steen 1986) . In Japan, zinc deficiency is diagnosed according to the Practice Guideline for Zinc Deficiency 2018, which sets four criteria for diagnosis, as follows: (a) one or more symptoms of zinc deficiency or low serum alkaline phosphatase, (b) exclusion of other diseases, (c) low serum zinc, and (d) alleviation of symptoms upon zinc administration. Serum zinc levels of <60 µg/dL indicate zinc deficiency, and 60–80 µg/dL indicate marginal deficiency (Kodama et al. 2018).

The guidelines recommends that patients with zinc deficiency should initially consume zinc-enriched foods, e.g., oyster, liver (beef, pig, and chicken), and beef. However, it is usually difficult to overcome zinc deficiency through diet alone.

In March 2017, the indication for zinc acetate dihydrate (NOBELZIN®, Nobelpharma Co., Ltd., Tokyo, Japan) was expanded from Wilson's disease to include hypozincemia. The guidelines recommend that when dietary therapy is insufficient, a zinc preparation be administered at a dosage of 50–100 mg/day for adults and 1–3 mg/kg/day for children (Kodama et al. 2018). Due to the diverse clinical symptoms of zinc-deficiency/hypozincemia, zinc acetate dihydrate is prescribed in various clinical departments, including dermatology, pediatrics, gastroenterology, nephrology, and general medicine.

Five years has passed since the approval of zinc acetate dihydrate for hypozincemia treatment in Japan by the Health, Labour and Welfare Ministry. Therefore, we conducted this post-marketing study (PMS) to examine the true picture of the prescription, safety, and effectiveness of zinc acetate dihydrate 25 mg/50 mg/granulated powder.

2. Investigations and results

2.1. Participants

For this multicenter PMS, 1009 patients were enrolled from 230 sites across Japan. From the 1009 registered patients, 995 forms were retrieved. Among the 995 patients who submitted forms, 67 were excluded from analysis population: 4 were registered outside of the survey period, 10 were registered more than two weeks after starting administration, and 57 did not attend any visit after the first visit. Therefore, the safety analysis set (SAS) included 928 patients. For the analysis of effectiveness, 767 patients were included. Reasons for patient exclusion from this analysis were

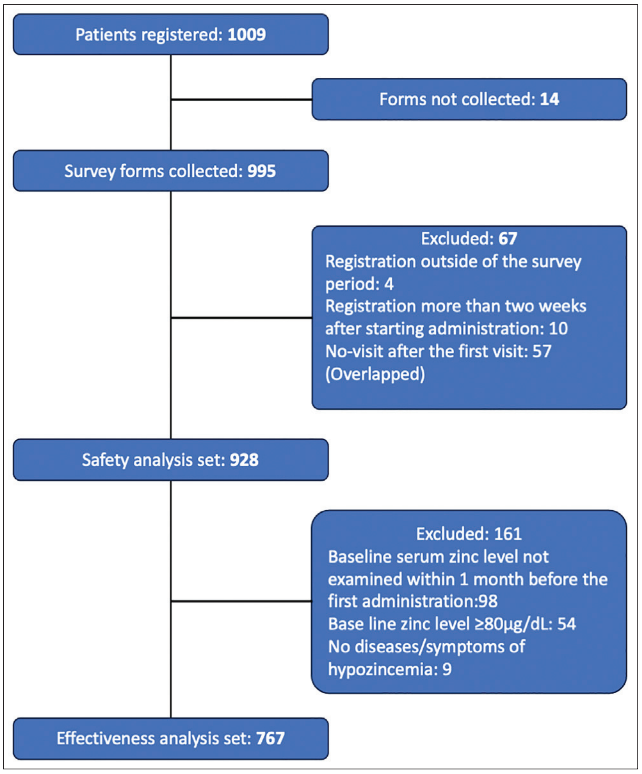

Fig. 1: Schematic outline of the data collection and analysis.

as follows: serum zinc concentration was not assessed within one month before starting administration (98 patients), zinc concentration was ≥80 μg/dL at baseline (54 patients), and lack of hypozincemia-associated diseases or symptoms at baseline (9 patients). Figure 1 presents a flowchart of patient enrollment.

Table 1 presents the demographics and baseline characteristics of patients in the SAS and in the efficacy analysis set (EAS). In the SAS, 59.6% (553/928) were female and 40.4% (375/928) were male. With regards to age, 11.3% (105/928) were under 16 years old, 23.5% (218/928) were ≥16 and <65 years old, and 65.2% (605/928) were ≥65 years old. Comorbidities, other than diseases or symptoms associated with hypozincemia, were present in 70.0% (650/928) of patients at baseline, and 16.1% (149/928) and 13.7% (127/928) of patients had renal and hepatic dysfunction, respectively.

The most frequent mean daily dose was ≥50 mg and <100 mg, which was taken by 55.9% (519/928) of patients. During the 52-week observation period, the most common dosing period was 52 weeks (37.7%; 350/928), followed by <12 weeks (25.3%; 235/928). Within the 52-week study period, 61.3% (569/928) of patients discontinued zinc acetate dihydrate treatment for the following reasons: "improved" (27.9%), "completely cured" (20.2%), "developing AEs" (14.6%), and "no visit to hospital" (13.7%) (Table 2).

2.2. *Safety evaluation*

During the 52 weeks after initiating zinc acetate dihydrate administration, the overall incidence of ADRs was 9.4% (87/928). The most common ADR was copper deficiency (2.4%), followed by nausea (1.4%), and abdominal discomfort (1.0%). Among 928 patients, 19 (2%) developed serious ADRs (sADRs), including copper deficiency (n=11, 1.2%); blood copper decreased (n=3, 0.3%); and anemia, cytopenia, sinus node dysfunction, enterocolitis, gastric ulcer hemorrhage, and lipase increased (n=1 each) (Table 3). These incidence rates were lower than observed in the pre-approval clinical tests in Japan. For the time of onset of ADRs, rates of ADRs within 12 weeks was the highest, and did not show the tendency to increase by long-term use.

Table 1: Patients' demographics and baseline characteristics

Patients' demographics	SAS (n=928) n (%)	EAS (n=767) n (%)
Gender		
Male	375 (40.4)	303 (39.5)
Female	553 (59.6)	464 (60.5)
Age		
Mean ± SD	64.6 ± 24.6	63.9 ± 25.3
<16 years	105 (11.3)	93 (12.1)
≥16 to <65 years	218 (23.5)	172 (22.4)
≥65 years	605 (65.2)	502 (65.4)
Disease duration of hypozincemia		
<30 days	788 (84.9)	686 (89.4)
≥30 to <90 days	76 (8.2)	39 (5.1)
≥90 to <360 days	32 (3.4)	21 (2.7)
≥360 days	14 (1.5)	9 (1.2)
UNK	18 (1.9)	12 (1.6)
Inpatient / Outpatient (at the first dose)		
Inpatient	63 (6.8)	60 (7.8)
Outpatient	865 (93.2)	707 (92.2)
Allergic history		
No	750 (80.8)	615 (80.2)
Yes	147 (15.8)	124 (16.2)
Presence of comorbidities		
No	278 (30.0)	232 (30.2)
Yes	650 (70.0)	535 (69.8)
Presence of renal dysfunction		
No	779 (83.9)	648 (84.5)
Yes	149 (16.1)	119 (15.5)
Presence of hepatic dysfunction		
No	801 (86.3)	664 (86.6)
Yes	127 (13,7)	103 (13.4)

SD standard deviation
UNK unknown

In the SAS, we analyzed factors affecting the safety of zinc acetate dihydrate treatment. The incidence of ADRs was significantly higher in patients with comorbidities compared to those without (10.8% vs 6.1%, p=0.025). And incidence of ADRs in patients with renal dysfunction were higher than those without (14.8% vs 8.3%, p=0.013), and those with/without hepatic dysfunction (16.5% vs 8.2%, p=0.002). Notably, in the subgroup analysis according to total dose, the rate of ADR occurrence was lowest in the maximum dose; "36400 mg" group (3.6%), and a higher total dose tended to lead to lower incidence rate of ADRs (p=0.032, C-A test). Similarly, accordance with real dosing duration, the longer real dosing periods resulted in the lower incidence rates of ADRs with p=0.002 (Table 4, upper columns).

2.3. *ADRs of special interest*

Copper deficiency and pancreatitis have been identified as important risks of zinc acetate dihydrate treatment in the risk-management plan (RMP) by the Pharmaceuticals and Medical Devices Agency (PMDA), and were defined as ADRs of special interest in our present study. However, there was no incidence of pancreatitis, and only 4/928 patients exhibited an elevated serum lipase level as an ADR.

Table 2: Dosing status

Dose and dosing duration	SAS (n=928) n (%)	EAS (n=767) n (%)
Mean one-day dose		
<50 mg	206 (22.2)	166 (21.6)
≥50 to <100 mg	519 (55.9)	426 (55.5)
≥100 mg	203 (21.9)	175 (22.8)
Total dosage		
<8400 mg	396 (42.7)	327 (42.6)
≥8400 to <16800 mg	232 (25.0)	193 (25.2)
≥16800 to <25200 mg	220 (23.7)	176 (22.9)
≥25200 to <36400 mg	25 (2.7)	20 (2.6)
≥36400 mg	55 (5.9)	51 (6.6)
Real dosing duration		
<12 weeks	235 (25.3)	200 (26.1)
≥12 to <24 weeks	181 (19.5)	146 (19.0)
≥24 to <36 weeks	92 (9.9)	77 (10.0)
≥36 to <52 weeks	70 (7.5)	53 (6.9)
52 weeks	350 (37.7)	291 (37.9)
Dosing status		
Not discontinued	359 (38.7)	
Discontinued	569 (61.3)	
Reason for discontinuation		
Completely cured	115 (20.2)	
Improved	159 (27.9)	
No change	50 (8.8)	
Progressed	1 (0.2)	
Developing AEs	83 (14.6)	
No visit	78 (13.7)	
Change of hospital	44 (7.7)	
Others	45 (7.9)	
Restart		
No	912 (98.3)	
Yes	16 (1.7)	

Table 3: Adverse drug reactions (ADRs) and serious ADRs (sADRs)

ADRs	n (%)
Safety analysis population	928
Patients with ADRs	87 (9.4)
ADRs: n	99
Copper deficiency	22 (2.4)
Abdominal discomfort	9 (1.0)
Nausea	13 (1.4)
Investigational abnormality	12 (1.3)
Blood copper decreased	3 (0.3)
Lipase increased	4 (0.4)
Blood alkaline phosphatase increased	6 (0.6)
sADRs	
Safety analysis population	928
Patients with sADRs	19 (2.0)
sADRs; n	20
Anaemia	1 (0.1)
Cytopenia	1 (0.1)
Copper deficiency	11 (1.2)
Sinus node dysfunction	1 (0.1)
Enterocolitis	1 (0.1)
Gastric ulcer hemorrhage	1 (0.1)
Blood copper decreased	3 (0.3)
Lipase increased	1 (0.1)

The incidence of copper deficiency was 2.7% (25/938), including 14 subjects who were diagnosed as having serious disease, as described above. Among the patients with copper deficiency, 92% were >65 years old, and all patients with serious copper deficiency were >65 years old. Moreover, all 25 subjects with copper deficiency had complications at baseline, such as cardiac diseases, hypertension, diabetes mellitus, and digestive apparatus diseases. Additionally, 13/25 subjects had renal diseases and 9/25 had hepatic diseases (2 overlapping) (Table 4, lower columns).

2.4. Effectiveness

Physicians evaluated the effectiveness of zinc acetate dihydrate treatment based on the change of serum zinc levels, and changes in the diseases and symptoms associated with hypozincemia, using three categories: "effective", not effective", and "indeterminate". Of the 767 patients in the EAS, 688 subjects were analyzed, excluding those without available data. As shown in Table 5, the overall efficacy rate was 83.0% (480 "effective"/578 "effective" + "not effective" excluding "indeterminate"). Among subgroups according to dosing duration, the efficacy rate was 82.3% in "<12 weeks", 86.0% in "≥12 and <24 weeks", 90.5% in "≥24 and <36 weeks", 72.9% in "≥36 and <52 weeks", and 82.1% in "52 weeks". The efficacy rate was >80% in all subgroups except "≥36 and <52 weeks". These data indicated that the majority of patients experienced sufficient beneficial effects within the first 12 weeks, and these effects were sustained for longer than 52 weeks. Mean efficacy rates of >75% were obtained in subgroups classified according to gender, age, and duration of hypozincemia. The efficacy rate was significantly lower in patients with renal dysfunction, than in patients without renal dysfunction (73.1% vs 84.9%, p=0.005). Similarly, the efficacy rate was significantly lower in patients with hepatic disease (69.2%; 45/65) than in patients without hepatic dysfunction (84.8%; 435/513) (p=0.001). Overall, serum zinc levels were elevated from 59.13 µg/dL on average at baseline, to >90 µg/dL within 12 weeks, and the higher levels were maintained during the observation period (Fig. 2). In the groups of patients with and without renal comorbidities, the mean zinc levels were elevated from 54.56 µg/dL and 60.24 µg/dL, respectively, at base line, to 95.05 µg/dL and 96.51 µg/dL, respectively, at the end of the observation period. Among patients with and without hepatic complications, the mean zinc levels were elevated from 52.88 µg/dL and 60.36 µg/dL to 93.24 µg/dL and 96.81 µg/dL, respectively. Therefore, regardless of the presence or absence of these complications, treatment raised serum zinc levels to within the reference range (data not shown).

Next, we evaluated the efficacy with regards to each hypozincemia-associated disease or symptom. Overall, 207 patients had taste disorder, 112 anorexia, 65 anemia, 53 dermatitis, and 48 stomatitis. Table 5 presents the efficacy rates according to diseases and symptoms. Among the digestive apparatus diseases, the efficacy rate was highest for stomatitis (87.5%; 42/48), followed by taste disorder (87.4%; 181/207), anorexia (86.6%; 97/112), and others including glossalgia (80%; 4/5). Among the cutaneous diseases, the efficacy rates were 96.2% (25/26) for pressure ulcer, and 86.8% (46/53) for dermatitis. For pediatric developmental issues, efficacy rates of 66% were achieved for both poor weight gain and short stature.

Table 4: Adverse drug reactions (ADRs) and copper deficiency in subgroups

Insidence of ADRs	n (% in SAS)	χ^2 test
Comorbidities		
No	17 (6.1)	p=0.025*
Yes	70 (10.8)	
Renal dysfunction		
No	65 (8.3)	p=0.013*
Yes	22 (14.8)	
Hepatic dysfunction		
No	66 (8.2)	p=0.002*
Yes	21 (16.5)	
Total dose of zinc acetate dihydrate		
<8400mg	46 (11.6)	p=0.002*
≥8400 to <16800 mg	23 (9.9)	
≥16800 to <25200 mg	10 (4.5)	
≥25200 to <36400 mg	6 (24.0)	
≥36400 mg	2 (3.6)	
Real dosing period		
<12 weeks	28 (11.9)	p=0.018*
≥12 to <24 weeks	22 (12.2)	
≥24 to <36 weeks	11 (12.0)	
≥36 to <52 weeks	8 (11.4)	
52 weeks	18 (5.1)	

Copper deficiency (including reduced blood copper concentration)	n (% in 25)
All over	25
Age	
<65 years	2 (8.0)
≧65 years	23 (92.0)
Comorbidities	
No	0 (0.0)
Yes	25 (100.0)
Renal dysfunction	
No	12 (48.0)
Yes	13 (52.0)
Hepatic dysfunction	
No	16 (64.0)
Yes	9 (36.0)

* means significant difference

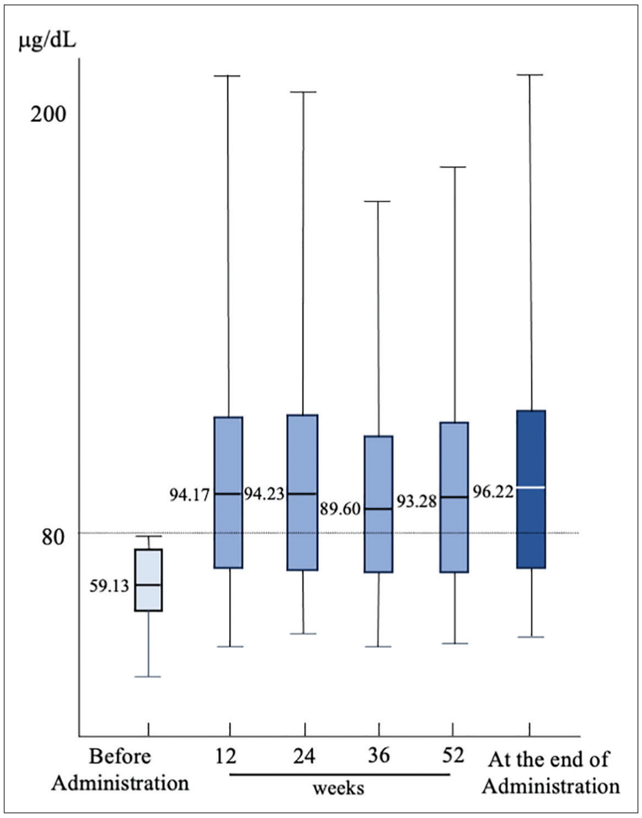

Fig. 2: Change of serum zinc concentration. Box plot shows the serum zinc concentration at each indicated time-point. Horizontal lines in each box represent the 25th percentile, median, and 75th percentile, respectively. The whiskers extend to the minimum and maximum points.

Most of the diseases and symptoms were largely recovered within 12 weeks and, after that, efficacy rates were elevated by degrees (data not shown).

3. Discussion

This survey included hypozincemia patients who were administered zinc acetate dihydrate, and thus the demographics of the enrolled patients reflect this patient population. The largest age group comprised subjects >60 years old, especially of 70–80 years of age, suggesting the tendency of malnutrition among elderly persons. On the other hand, over two-thirds of the SAS had some complication, suggesting that hypozincemia could arise from various diseases. Overall, patients with renal disfunction, hepatic disfunction, or diabetes mellitus are more likely to have zinc deficiency. Serum zinc levels should be monitored in these patients, and rapid supplementation administered in cases exhibiting zinc shortage. On the other hand, zinc shortage in childhood can lead to growth retardation, movement disorder, and mortality, which presents a serious challenge in developing countries (Gibson 2000). Notably, childhood malnutrition is not unusual in Japan. Zinc deficiency can occur due to low zinc levels in preterm infants, low zinc in the mother's milk, or refractory diarrhea. In our present study, 10% of SAS were subjects under the age of 16 years, suggesting the importance of zinc supplementation in the nutrition management of children.

It has been reported that zinc inhibits the gastrointestinal absorption of copper, potentially leading to copper deficiency (Wapnir and Balkman 1991). In our present PMS, the most frequent ADR was copper deficiency (2.4%), although the incidence was lower than that observed in the phase II test in Japan. The risk of copper deficiency is stated on the package insert for zinc acetate dihydrate, and appropriate monitoring of serum copper concentration in suggested in after-marketing information. Most of the patients who exhibited copper deficiency were elderly, and all had some primary diseases, suggesting that it may be necessary to adjust the dose and regimen in these patients. At the onset of copper deficiency, most patients had serum zinc concentrations under the upper limit of the normal range. Notably, no incidence of copper deficiency was observed in subjects aged <16 years, which is consistent with previous results reporting the safety of zinc supplementation in childhood (Ito et al. 2021).

Furthermore, the incidence rates of ADRs were not associated with the dosing periods nor with the total dosage of zinc acetate dihydrate, suggesting that the drug is free of cumulative toxicities. Zinc acetate dihydrate administration showed high efficacies in the overall patient population, regardless of background. Serum

Table 5: Efficacy in terms of zinc concentrations and diseases/symptoms

Efficacy in zinc concentration

	Effective n	Efficacy rate* %	p value	test
All over efficacy in EAS	480/578	83.0		
Real dosing duration				
<12 weeks	102/124	82.3		
≥12 to <24 weeks	98/114	86.0		
≥24 to <36 weeks	57/63	90.5		
≥36 to <52 weeks	35/48	72.9		
52 weeks	188/229	82.1		
Gender				
Male	178/226	78.8	p=0.027**	χ^2 test
Female	302/352	85.8		
Age				
<16 years	48/63	76.2	p=0.294	C-A test
≥16 to < 65 years	106/125	84.8		
≥65 years	326/390	83.6		
Disease duration of hypozincemia				
<30 days	440/526	83.7	p=0.121	C-A test
≥30 to <90 days	20/25	80.0		
≥90 to <360 days	11/15	73.3		
≥360 days	4/6	66.7		
Presence of comorbidities				
No	154/183	84.2	p=0.628	χ^2 test
Yes	326/395	82.5		
Presence of renal dysfunction				
No	412/485	84.9	p=0.005**	χ^2 test
Yes	68/93	73.1		
Presence of hepatic dysfunction				
No	435/513	84.8	p=0.001**	χ^2 test
Yes	45/65	69.2		

* Efficacy rate means "effective"/"effective" + "not effective" excluding "indeterminate"
** means significant difference

Efficacy in Diseases and Symptoms

	Effective n	Efficacy rate* %
Digestive apparatus disease		
Stomatitis	42/48	87.5
Anorexia	97/112	86.6
Taste disorder	181/207	87.4
Others (Glossalgia)	4/5	80.0
Cutaneous disease		
Dermatitis	46/53	86.8
Alopecia	10/14	71.4
Pressure ulcer	25/26	96.2
Pediatric growth disturbance		
Poor weight gain	4/6	66.7
Short statue	18/27	66.7
Systemic disability		
Compromise	7/11	63.6
Anemia	40/65	61.5
General malaise	14/18	77.8
Reproductive system disease		
Sexual dysfunction	0/0	–
Agenesis	0/0	–
Hepatic Dysfunction		
Cirrhosis	10/30	33.3
Hepatic encephalopathy	4/8	50.0
Hyperammonemia	1/11	9.1
Hypoalbuminemia	0/9	0
Others		
Fatigability	4/4	100.0

* Efficacy rate means "effective"/"effective" + "not effective" excluding "indeterminate"

zinc concentrations were up to within the standard range within 12 weeks after the first dose, and were sustained at a mean of >90 mg/dL, without excessive concentrations.

Although we did not test significant differences in serum zinc concentrations between patients with and without renal or hepatic dysfunctions, there were differences in the incidence rates of hypozincemia-associated diseases or symptoms. Notably, the efficacy in the recovery from anemia was inferior among patients with renal dysfunction compared to those without. It can be assumed that in these cases, the cause of anemia was complicated, including renal dysfunction itself, such that it could not be improved by only an increase of zinc concentration. On the other hand, stomatitis, taste disorder, and dermatitis were efficiently improved, even in the subjects with renal dysfunction, suggesting that these symptoms were directly caused by hypozincemia. With regards to anemia and other diseases and symptoms, the efficacies did not significantly differ between the groups of patients with versus without hepatic dysfunction. On the other hand, the efficacy rates for symptoms of hepatic dysfunction—including cirrhosis, hepatic encephalopathy, hyperammonemia, and hypoalbuminemia—were lower than for other symptoms, which diminished the overall efficacy rate in the population with hepatic dysfunction. Nevertheless, efficacy rates of 30% and 50% were achieved in cirrhosis and hepatic encephalopathy, respectively, suggest that hypozincemia is deeply associated with hepatic dysfunction, such that its recovery can lead to the improvement of hepatic function, as mentioned in multiple previous reports (Nishikawa et al. 2022; Bloom et al. 2021). It has also been reported that hypozincemia is associated with the development of renal diseases and diabetes mellites, as well as hepatic dysfunction, and that zinc supplementation can restore these diseases (Nakatani et al. 2021; Cooper-Capetini et al. 2017). In the present study, the number of subjects with disease was rather small, and we could not elucidate the involvement of zinc deficiency in the development of various diseases. This topic should be further explored by clinical studies and analyses of real world data (RWD).

Zinc is an essential nutrient for fetal and neonatal growth, as well as for brain growth and development (Brion et al. 2021). Moreover, some studies have reported that zinc is involved in growth hormone secretion (Nasiadek et al. 2020) and it is widely known that zinc deficiency in early infancy can lead to short height and low weight. In the present survey, the number of enrolled children with short height or low weight was not sufficient for analysis; however, zinc acetate dihydrate was assessed as effective in two-thirds of these patients, which is a significant outcome. Zinc deficiencies might be frequently overlooked due to the many other factors contributing to growth deficits in infancy and early childhood-including chromosomal abnormalities, infections, and poor nutrition. However, to support well-being later in life, hypozincemia should be diagnosed and corrected as early as possible.

Since NOBELZIN® has been launched in 2017, this drug has been widely used in patients. The findings of the present PMS of four years support that zinc acetate dihydrate has been safely used in a wide range of patients, and that it shows effectiveness for various diseases and symptoms. Further elucidation of the associations between zinc and various pathological conditions will additionally increase the clinical importance of zinc preparations.

4. Experimental

4.1. Study design and participants

In this multicenter PMS, we conducted a specific drug use survey of zinc acetate dihydrate for the treatment of hypozincemia in Japan. The surveillance period was between December 2017 and December 2021, with patients registered between December 2017 and March 2019. Participants were patients with hypozincemia who were firstly administered zinc acetate dihydrate during the registration period, and who had hypozincemia-associated diseases or symptoms. The study was conducted in accordance with the Good Post-marketing Study Practice (GPSP) requirements defined by the Japanese Ministry of Health, Labour and Welfare (Ministry of Health, Labour and Welfare, Ministerial Ordinance on Good Post-marketing Study Practice for Drugs. No. 171, December 20, 2004)

4.2. Data collection

We used electronic data capture (EDC) to collect data regarding patient background factors, status of administration, clinical course (including laboratory results), adverse events (AEs), adverse drug reactions (ADRs; events for which a causal relationship with this drug could not be excluded), and evaluation by doctors.

4.3. Safety evaluation

We investigated AEs occurring during the first 52 weeks after initiating zinc acetate dihydrate treatment or up to the date of discontinuing the therapy. AEs and adverse drug reactions ADRs were classified based on the preferred terms and system organ class, according to the Medical Dictionary for Regulatory Activities/Japanese version MedDRA/J ver. 25. We evaluated the existence, severity, outcome, and duration of ADRs; laboratory data associated with ADRs; and causal relationships. ADRs of special interest, including copper deficiency and pancreatitis, were also evaluated. Factors contributing to the occurrence of ADRs were evaluated using the Chi-squared (χ^2) test, and the Cochran-Armitage (C-A) test was also employed for ordinal scale, with a two-sided significance level of 5%.

4.4. Efficacy evaluation

The efficacy of treatment with zinc acetate dihydrate was evaluated for each hypozincemia-associated disease or symptom, at 52 weeks after treatment initiation or at the time of withdrawal/dropout. The following three-point scale was used: "effective", "not effective", or "not evaluable". Efficacy for hypozincemia was also determined using the same three-point scale. The χ^2 test was used to evaluate the efficacy rate, and the C-A test was used for ordinal scale.

Conflicts of interest: none declared

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