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Survey on the use of zinc sulfate in parenteral nutrition in spanish hospitals

Encuesta sobre el uso del sulfato de zinc en nutrición parenteral en los hospitales españoles

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Abstract

Objective: In certain situations parenteral nutrition subsidiary patients may have an increase in zinc demand (Zn). The objective of the study was to know the scope of the use of Zn sulfate in patients with parenteral nutrition in Spanish hospitals.

Method: A survey was designed focusing on the incorporation of Zn sulfate into parenteral nutrition, under real practice conditions, in the adult and pediatric population. We asked about the number of parenteral nutrition supplemented with zinc in the last year, by the doses used, and the situations in which it was added to parenteral nutrition formula. The survey was conducted by telephone interview to the pharmacists responsible for the parenteral nutrition units.

Results: A total of 53.9% (n = 69) of the contacted hospitals responded to the survey. 60.9% incorporated Zn sulfate into the parenteral nutrition of adults, and 76.2% used it in pediatric patients. In adults, 31.1% used Zn to complete the dose provided by the solution of trace elements, 46.7% supplemented Zn in patients with high intestinal losses, and 28.6% did it in critically ill patients with a high degree of metabolic stress. The majority supplementation regimen was 10 mg/day (55.6%). In the pediatric population Zn ampules were used mainly in preterm infants, with the most used doses being 200 mcg/kg/day and 400 mcg/kg/day (42.6% and 23.4%, respectively).

Conclusions: The use of zinc sulfate in adult parenteral nutrition to complete the dosages suggests that solutions of trace elements could be deficient in Zn. Its use as a supplement in adult parenteral nutrition is not an extended practice in specialized nutritional support protocols in Spanish hospitals, highlighting its low employment in patients with significant catabolism.

KEY WORDS
Zinc; Trace elements; Parenteral nutrition; Drug utilization; Practice standards.

Resumen

Objetivo: En determinadas situaciones, los pacientes subsidiarios de nutrición parenteral pueden tener un incremento en la demanda de zinc (Zn). El objetivo del estudio fue conocer el alcance de la utilización del sulfato de Zn en pacientes con nutrición parenteral en los hospitales españoles.

Método: Se diseñó una encuesta centrada en la incorporación del sulfato de Zn en nutrición parenteral, en condiciones de práctica reales, en la población adulta y pediátrica. Se preguntó por el número de nutrición parenteral suplementadas con zinc en el último año, por las dosis utilizadas, así como por las situaciones en las que se añadía a la fórmula de nutrición parenteral. La encuesta se realizó mediante entrevista telefónica a los facultativos responsables de las unidades de nutrición parenteral.

Resultados: Respondieron a la encuesta el 53,9% (n = 69) de los hospitales contactados. El 60,9% incorporó sulfato de Zn en la nutrición parenteral de adultos, y el 76,2% lo empleó en pacientes pediátricos. En adultos, el 31,1% lo utilizó para completar la dosis aportada por la solución de oligoelementos, el 46,7% suplementó Zn en pacientes con pérdidas intestinales elevadas y el 28,6% en pacientes críticos con alto grado de estrés metabólico. La pauta de suplementación mayoritaria fue la de 10 mg/día (55,6%). En la población pediátrica, las ampollas de Zn se emplearon principalmente en los neonatos pretérmino, siendo las dosis más utilizadas las de 200 mcg/kg/día y 400 mcg/kg/día (42,6% y 23,4%, respectivamente).

Conclusiones: El empleo de sulfato de zinc en la nutrición parenteral de adultos para completar las dosis sugiere que las soluciones de oligoelementos podrían ser deficitarias en Zn. Su uso como suplemento en la nutrición parenteral de adultos no constituye una práctica extendida en los protocolos de soporte nutricional especializado en los hospitales españoles, destacando su bajo empleo en pacientes con catabolismo importante.

PALABRAS CLAVE
Zinc; Micronutrientes; Nutrición parenteral; Utilización de fármacos; Estándares de práctica.

Introduction

Zinc is an essential micronutrient in human nutrition. Among many biological roles, it is essential to the functioning of the immune system and participates in the oxidative stress response, wound healing, the sense of taste, and glucose homeostasis[1].

There are a number of situations or diseases that predispose to zinc deficiency, either by increased gastrointestinal losses, decreased gastrointestinal absorption, or increased demand[2]:

- Gastrointestinal disease (decreased absorption or increased losses): Malabsorption syndromes (inflammatory bowel disease, short bowel syndrome, bariatric surgery), enteric fistulas, chronic diarrhea, enterostomy.
- Infectious processes and, in general, any inflammatory process.
- Burns (skin loss).
- Increased anabolic demand.

The assessment of body zinc status is difficult. After several weeks of insufficient intake, homeostatic mechanisms keep plasma zinc concentrations stable (80-120 µg/dL [12-18 µmol/L]), and therefore these concentrations do not reflect nutritional status[3]. In fact, variations of less than 30% in plasma concentrations are not considered to be significant[2]. As a result, plasma zinc concentrations are a poor marker of deficiency, because they only change when there is a marked decrease in zinc stores. In addition, plasma zinc concentrations are reduced in inflammatory processes due to redistribution. C-reactive protein (CRP) concentrations of 100 to 200 mg/L are associated with a 40% to 60% decrease in plasma zinc concentration[4]. Therefore, the determination of CRP in conjunction with zinc concentrations is recommended for their assessment[5,6], because only at CRP concentrations of less than 20 mg/L can plasma zinc concentrations be used as markers of body zinc status.

The most recent guidelines recommend the following dosage regimens in adult patients with Parenteral Nutrition (PN):

- Patients without gastrointestinal losses: administer 3 to 4 mg/d (ASPEN 2012)[7]or 2.5 to 6.5 mg/d (ESPEN 2009)[8,9] of zinc to fulfil the recommended daily intake.
- Patients with significant gastrointestinal losses (fistulas, diarrhea): supplement with 12 mg/d of zinc per liter of gastrointestinal losses in fasting conditions[1].
- Patients with severe catabolic disorder: supplement with 2 to 4 mg/d of zinc[10,11].
- Patients at risk of refeeding syndrome: loading dose of 10 to 30 mg of zinc, followed by a daily maintenance dose[12].

The macronutrient solutions used in PN do not contain zinc as a contaminant, so it must be supplemented from the start of treatment in patients with total PN. There have been reports of zinc deficiency in patients with PN without additional zinc[13]. In adults, the recommended daily intake of zinc in adults is fulfilled by the addition to PN of trace-element solutions containing 3 to 6.5 mg of zinc per ampoule. Nevertheless, in conditions of increased demand or losses, supplemental zinc can be given in the form of zinc sulfate (i.v. 10 mg/mL ampoules), which is marketed as a magistral preparation in Spain by the Fresenius-Kabi laboratory.

The objective of the present study was to determine the use of zinc sulfate ampoules in patients with PN under real practice conditions in Spanish hospitals.

Methods

A survey was designed to evaluate the use of zinc sulfate in adult and pediatric patients with PN under real practice conditions. Questions addressed the routine use of trace-element solutions in adult and pediatric PN, the number of adult and pediatric PN formulations supplemented with zinc sulfate ampoules used in the previous year, the dose of supplemental zinc used in adult and pediatric patients, and the situations in which supplemental zinc was used in both groups (Table 1).

The manufacturer of the zinc sulfate ampoules (Fresenius-Kabi) was asked to list the Spanish hospitals that purchased these ampoules in 2013. All these hospitals were contacted in 2014. The survey was conducted by telephone interview with the pharmacists responsible for the PN units in each hospital.

Table 1. Questions asked in the telephone survey

1. Do you usually incorporate trace-element solutions in adult and pediatric parental nutrition?
2. In addition to trace-element solutions, does the parenteral nutrition protocol incorporate additional zinc sulfate? If so:
3. In what situations/processes is zinc sulfate used?
4. What is the dose of zinc sulfate used in these circumstances in adult and pediatric patients?
5. How many parental nutrition formulations (adult and pediatric) included zinc sulfate in the previous year?

Data analysis was conducted using descriptive techniques, calculating the absolute and relative frequencies (percentages) of the variables.

Results

Based on the information provided by the manufacturer, the 128 hospitals that purchased zinc sulfate ampoules in 2013 were contacted by telephone. In total, 69 hospitals responded (53.9%) to the survey. The remaining hospitals declined to respond to the survey, or they answered the initial questions, but did not provide the number of PN formulations supplemented with zinc used in the last year, referring to a lack of time or difficulty in obtaining this information. The distribution of the responding hospitals based on the number of beds was similar to the percentage distribution of the hospitals contacted. Thereby, 55% of the contacted hospitals had 500 or more beds, 29% had between 200-499 beds, while 16% had less than 200 beds. Regarding the responding hospitals, 56.5% had 500 or more beds, 23% had between 200-499 beds, and, finally, 20% had less than 200 beds.

All responding hospitals reported that they routinely used trace-element solutions in PN. A total of 49 673 adult and 29 642 pediatric PN formulations were prepared in the hospitals which incorporated zinc sulfate during 1 year. 60.9% of the hospitals (n = 42) reported that they used zinc sulfate ampoules in the preparation of adult PN as established in the hospital protocol. 76.2% (n = 45) of the 59 hospitals with pediatric units reported that they used zinc sulfate in the preparation of neonatal and pediatric PN.

Zinc sulfate was used more often in university hospitals than in non-university hospitals, both in adults (74% vs 45%) and in pediatric patients (71% vs 58%). The stratified analysis of the results according to hospital size showed that 74% and 77% of hospitals with more than 500 beds included zinc sulfate in adult and pediatric PN protocols, respectively. 56% of hospitals with 200 to 500 beds and 29% of hospitals with fewer than 200 beds used zinc sulfate in adult PN protocols, respectively, whereas 73% of hospitals with 200 to 500 beds and 80% of hospitals with fewer than 200 beds used zinc sulfate in pediatric PN protocols, respectively (Table 2).

Fixed doses of zinc were mainly used in adult patients (83.3%), whereas doses were adjusted to plasma levels or the volume of gastrointestinal losses in the remaining patients (Table 3). In the pediatric population, the zinc dose was always adjusted to patient weight: 90% of hospitals reported using fixed doses by weight (Table 4), whereas 10% of the hospitals stratified zinc sulfate dose by patient weight as well as age group (preterm newborn, infant, child).

The hospitals reported the use of zinc supplements in adults in the following conditions:

- Patients with significant gastrointestinal losses (high-output fistulae, diarrhea): 46.7% of hospitals.
- In all patients, to supplement the dose of zinc provided by the multi-trace element solution: 31.1% of hospitals
- Critically ill patients with severe metabolic stress: 28.6% of hospitals.
- Patients receiving home PN: 8.9% of hospitals
- Zinc plasma levels below normal range: 6.7% of hospitals.
- In patients with malabsorption syndromes (inflammatory bowel disease, short intestine syndrome): 6.7% of hospitals

Table 2. Stratified analysis of the incorporation of zinc sulfate in PN in adult and pediatric patients

		Number of hospital beds		
Adults		**> 500 (n = 39)**	**200-500 (n = 16)**	**< 200 (n = 14)**
Zn added to NP	Yes	74%	56%	29%
	No	26%	44%	71%
Dosage of zinc	10 mg/d	62%	45%	25%
	5 mg/d	10%	22%	25%
	3 mg/d	10%	11%	25%
	2 mg/d	4%	-	-
	Variable*	14%	22%	25%
Pediatric patients		**> 500 (n = 39)**	**200-500 (n = 15)**	**< 200 (n = 5)**
Zn added to NP	Yes	77%	73%	80%
	No	23%	27%	20%
Dosage of zinc	<200 µg/kg/d	23%	9%	25%
	200 µg/kg/d	40%	36%	75%
	300 µg/kg/d	17%	9%	-
	400 µg/kg/d	20%	46%	-

*Depending on plasma levels or volume of gastrointestinal losses.
PN, parenteral nutrition; Zn, zinc.

Table 3. Zinc supplementation protocols used in adult parenteral nutrition (n=42)

Adult Supplementation Protocols	Hospitals (%)
10 mg/d	55.6%
5 mg/d	13.9%
3 mg/d	11.1%
2 mg/d	2.7%
Depending on the plasma levels or volume of intestinal losses	16.7%

Table 4. Fixed zinc supplementation protocols used in pediatric patients (n = 45)

Fixed zinc supplementation protocols in pediatric patients	Hospitals (%)
< 200 µg/kg/d	21.3%
200 µg/kg/d	42.6%
300 µg/kg/d	12.7%
400 µg/kg/d	23.4%

In the pediatric population, zinc sulfate ampoules were generally used in low-birth-weight preterm infants.

Discussion

Based on the information provided by the manufacturer, it appears that the incorporation of zinc sulfate in PN is not generally established in the artificial nutritional support protocols of Spanish hospitals. It was only used in 128 of the 565 hospitals (22.7%) included in the 2013 National Catalog of Hospitals, which includes hospitals with general, surgical, maternity-infant, oncologic, traumatic, or medical-surgical care activity[14]. Although this study did not address the acquisition of zinc sulfate ampoules from other manufacturers or the possibility of hospitals preparing their own magistral preparations, these situations are exceptional and only occur in a minority of cases. Thus, we consider that this apparent limitation does not affect the results obtained. However, only 54% of the contacted hospitals responded to the survey and this aspect may represent a limitation when extrapolating the conclusions to all Spanish hospitals.

In the Spanish market in 2013, there were no shortages of trace-element solutions that required the use of zinc sulfate ampoules to fulfil the recommended daily intake for zinc in patients with PN. Therefore, it could initially be assumed that the use of these ampoules was restricted to the administration of zinc supplements in patients with PN. However, almost one-third of the hospitals surveyed (31.1%) reported using zinc sulfate ampoules to supplement the dose provided by the trace-element solution. In Spain, commercially available trace-element solutions for adults contain from 3 to 6.5 mg of zinc per 10 mL. Thus, according to the trace-element solution used and the practice guidelines applied, zinc sulfate ampoules may be needed to meet the daily recommended intake. Thus, strictly speaking, rather than supplemental zinc being provided, the minimum recommended daily intake is being met. The results suggest that a large proportion of the responding hospitals consider the amount of zinc in commercially available trace-element solutions to be insufficient, pointing to the need to review the content of these trace-element solutions to adapt it to current recommendations.

46.7% of the hospitals surveyed reported using zinc sulfate to supplement PN in adult patients with high gastrointestinal losses (the more frequent dose used was 10 mg/d). The recommendation to use supplemental zinc as a function of the volume of gastrointestinal losses was based on studies conducted in 1979 by Wolman et al[15], who found a positive correlation between the amount of zinc lost in the gastrointestinal tract and the volume/weight of gastrointestinal losses. In patients with total PN, they recommended 12 mg of supplemental zinc per liter of losses due to high small bowel fistulas or jejunostomies, and 17 mg per liter of stool, both measured under fasting conditions:

$$\text{Zinc replacement (mg/d)} = 2 + 17\beta + 12\delta$$

where 2 = replacement for urinary losses
β = kg of feces or ostomy output (diarrhea)
δ = kg of losses via fistula or duodenojejunocolostomy.

However, as the study did not include patients with high gastrointestinal losses, a positive balance was achieved with the administration of 12 mg/d of supplemental zinc. Thus, the current guidelines recommend 12 mg of supplemental zinc per liter of gastrointestinal losses due to diarrhea, stoma, or enteric fistulas under fasting conditions[1].

In critically ill patients, decreased plasma zinc concentrations are inversely related to the magnitude of the inflammatory response[16]. These de-

creased concentrations may be due to systemic zinc redistribution as part of the acute phase response and to the systemic inflammatory response syndrome rather than to a real deficiency[5,17]. In septic patients, the use of zinc supplementation is controversial because in the same way that pathogenic microorganisms require iron, they also require zinc for their development and proliferation. In this situation, zinc supplementation could act against the redistribution mechanisms that allow low levels of zinc to be maintained in the pathogenic environment, although studies are needed to confirm this hypothesis[18]. Despite these issues, it has been postulated that zinc supplementation in septic patients could contribute to the prevention of the immunosuppression associated with zinc deficiency[19], although the optimal dose of zinc in this population remains unknown. For example, it has been shown that the administration of 30 mg/d of zinc to patients during the acute phase response may increase the febrile response associated with this situation[20]. In other critically ill patients, several studies have recommended the administration of 10 mg/d of zinc in polytrauma patients and up to 30 mg/d of zinc in burn patients[11,21-23]. In our study, 28.6% of the responding hospitals reported the use of supplemental zinc in critically ill patients: the typical dose used was 10 mg, which is in line with previous recommendations.

In patients with home PN, the provision of multi-trace element solutions is somewhat difficult, because their composition is not adapted to the needs of this group population. Specifically, the dose of manganese in trace-element solutions is much higher than that recommended in the current guidelines to prevent its accumulation in the brain[24]. The frequency of administration of these solutions should be reduced, for example, by their incorporation in PN every other day and by the use of zinc sulfate ampoules to fulfil the daily recommended intake of zinc. 7.5 mg/d of zinc would be sufficient to maintain adequate concentrations in patients with home PN, in the absence of short bowel syndrome, whereas 9.1 mg/d would be needed in patients with this disorder[25]. In our study, 8.9% (n = 6) of the responding hospitals reported the use of zinc sulfate ampoules in patients with home PN. Given that the NADYA Home and Ambulatory Artificial Nutrition Group reported that 34 hospitals used home PN in 2013[26], and that our study included 39 hospitals with more than 500 beds which, due to their size, increases their likelihood of using home PN, it may be inferred that the use of zinc sulfate ampoules to fulfil the recommended daily intake of zinc in this population is not a common practice. Obviously, this inference should be treated with caution because the data are not comparable, having been derived from records and voluntary communications in the case of the NADYA registry and hospital survey, respectively. Nevertheless, we highlight the need to investigate this aspect in greater depth.

In the pediatric population, zinc requirements are related to the growth rate and so supplemental zinc is administered according to age. Preterm neonates have a greater demand for zinc per kilo body weight (400 µg/kg/d), because two-thirds of body zinc is transferred from the mother during the last 10 to 12 weeks of gestation. Recommendations are for 250 µg/kg/d and 100 µg/kg/d for full-term neonates less than or more than 3 months of age, respectively, and 50 µg/kg/d (maximum 5000 µg/d) for children[27-29]. In neonates, zinc is the only trace element that should be added to PN from the first day, which explains the high percentage of responding hospitals that used zinc sulfate ampoules in pediatric PN (75.8%).

The pediatric trace-element solutions marketed in Spain provide 250 µg/mL of zinc (Peditrace®), the standard dose being 1 mL/kg/d. The responding hospitals reported that zinc ampoules were predominantly used in preterm neonates, the typical doses being 200 µg/kg/d and 400 µg/kg/d (42.6% and 23.4%, respectively). These data are in line with the results of a study conducted in 2011 in which 51% of hospitals routinely added zinc (in addition to that in trace-element solutions) to the PN of premature infants[30]. Although not explicitly requested by the survey, the data suggest that the recommendation of 200 µg/kg/d is used to fulfil zinc intake in pediatric trace-element solutions, and that 400 µg/kg/d is used when zinc is the only trace-element administered with PN.

A significant number of the responding hospitals used zinc sulfate in the PNs to complement the current commercially available trace-element solutions. This practice suggests that multi-trace-element solutions contain insufficient zinc, and thus their composition should be reviewed.

The use of zinc sulfate as a supplement in adult PN is not an extended practice that is routinely included in the specialized nutrition support protocols in Spanish hospitals. The most frequent use of zinc is as a supplement in patients with severe gastrointestinal losses. However, few hospitals use supplemental zinc as standard practice in critically ill patients and in patients with severe catabolic disorder, or individualize trace-element solutions in patients with home PN.

In contrast to the situation in adult patients, the use of zinc sulfate in the pediatric population is more widespread, either to complement the trace-element solution or to provide zinc as the only trace element in preterm neonates, which is in line with current recommendations.

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Conflict of interests

No conflict of interests.

Contribution to scientific literature

Zinc is an essential trace element that needs to be administered from the first day of treatment in patients on total PN. The recommended daily i.v. dose of zinc is met by the use of standard trace-element solutions. However, many situations are associated with an increased demand for this trace element, and standard solutions should be supplemented with zinc sulfate. Although the supplementation of zinc is widely described in the literature, protocols, and clinical practice guidelines, the extent to which the recommendations are applied in practice in Spain has remained unknown. The results of this study suggest that the recommendations are not consistently applied in daily practice, underscoring the need to encourage greater adherence to them in artificial nutrition protocols in hospitals.

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