Abstract: Central nervous system stimulants and drugs that suppress appetite Antidepressant drugs Lithium Drugs of abuse Hypnotics and sedatives Antipsychotic drugs Antiepileptic drugs Opioid analgesics and narcotic antagonists Anti-inflammatory and antipyretic analgesics and drugs used in gout General anesthetics and therapeutic gases Local anesthetics Neuromuscular blocking agents and skeletal muscle relaxants Drugs that affect autonomic functions or the extrapyramidal system Dermatological drugs, topical agents and cosmetics Antihistamines (H1 receptor antagonists) Drugs acting on the respiratory tract Positive inotropic drugs and drugs used in dysrhythmias Beta-adrenoceptor antagonists and antianginal drugs Drugs acting on the cerebral and peripheral circulations Antihypertensive drugs Diuretics Metals Metal antagonists Antiseptic drugs and disinfectants Penicillins, cephalosporins, other beta-lactam antibiotics, and tetracyclines Miscellaneous antibacterial drugs Antifungal drugs Antiprotozoal Drugs Antiviral drugs Drugs used in tuberculosis and leprosy Anthelminthic drugs Vaccines Blood, blood components, plasma and plasma products Formulations used in nutrition Drugs affecting blood coagulation, fibrinolysis, and hemostasis Gastrointestinal drugs Drugs that act on the immune system: cytokines and monoclonal antibodies Drugs that act on the immune system: immunosuppressive and immunostimulatory drugs Corticotrophins, corticosteroids, and prostaglandins Sex hormones and related compounds, including hormonal contraceptives Thyroid hormones, iodine, and antithyroid drugs Insulin, other hypoglycemic drugs, and glucagon Miscellaneous hormones Drugs that affect lipid metabolism Cytostatic drugs Radiological contrast agents Drugs used in ocular treatment Treatments used in complementary and alternative medicine Miscellaneous drugs and materials, medical devices and techniques.
Pregnancy  Oxidative stress may play a part in pre-eclampsia, and there is some evidence to suggest that supplements of vitamins C and E could reduce the risk. However, this remains unproven. The potential benefit of these antioxidants in 2410 women with a range of clinical risk factors has been evaluated in a large multicenter randomized, placebo-controlled trial \cite{1}. The women took vitamin C 1000 mg/day + vitamin E (RRR alpha tocopherol) 400 IU/day (n = 1199) or matched placebo (n = 1205) from the second trimester until delivery. The primary end-point was pre-eclampsia. Secondary end-points were low birth weight (under 2.5 kg) and small size for gestational age (below the 5th customized birth weight centile). The incidence of pre-eclampsia was similar in the two placebo (15% versus 16%; RR = 0.97; 95% CI = 0.80, 1.17). More low birth weight babies were born to women who took antioxidants than to controls (28% versus 24%; RR = 1.15; CI = 1.02, 1.30), but small size for gestational age did not differ between the groups (21% versus 19%; RR = 1.12; CI = 0.96, 1.31). The authors therefore concluded that concomitant supplementation with vitamins C and E does not prevent pre-eclampsia in women at risk, but does increase the rate of babies born with a low birth weight. They therefore recommended that the use of these high-dose antioxidants is not justified in pregnancy.

Susceptibility factors Liver disease  Water-soluble and fat-soluble vitamin formulations for addition to total parenteral nutrition solutions have historically been formulated separately. By the addition of glycocholic acid, a vitamin formulation (Cernevit™, Baxter, Heidelberg, Germany) has been developed that combines all the necessary vitamins in one vial. However, there is little information about the possible consequences of the administration of bile acids such as glycocholic acid, especially if there is pre-existing liver disease. The effects of total parenteral nutrition with a vitamin formulation containing high doses of glycocholic acid in patients with and without liver disease have been studied in a prospective, randomized, controlled trial in 74 patients, of whom 36 had hepatobiliary disease \cite{2}. They received total
parenteral nutrition for an average of 16 days, either with Cernevit or separate vitamin supplements. Serum glycocholic acid concentrations increased in the patients with liver disease treated with Cernevit, whereas total bile acids did not significantly change. Other liver function tests remained stable. There were no adverse events during Cernevit administration, except for a slight reversible increase in transaminases in one patient. The authors concluded that Cernevit was well tolerated after repeated dosing, even in patients with severe liver disease. They therefore recommended that, apart from standard controls of liver biochemistry, no specific surveillance is necessary during treatment with Cernevit. However, it should be noted that this was only a short-term study.

VITAMIN A (CAROTENOIDs) [SED-15, 3642; SEDA-28, 386]

**Drug overdose** Numerous vitamin supplements are available over the counter. Some are available as candy-like chewable formulations to encourage consumption by children. Three cases of overdose of such formulations have been reported [3A]. Each child had taken an estimated 200,000–300,000 IU of vitamin A. Their circulating vitamin A (retinol and retinyl palmitate) concentrations were monitored over 6 months. There were no clinical or biochemical complications. However, there were marked increases in both retinol and retinyl palmitate concentrations above the age-related reference ranges. In particular, it took 1–3 weeks for the serum retinol concentrations to peak and many months for them to normalize. The authors recommended that parents should be warned about the dangers of excessive vitamin A consumption. Clinicians should be aware of the late peak in serum retinol concentrations, which can lead to late complications of vitamin A overdose. There is a case for taking the chewable formulations off the market.

VITAMINS OF THE B GROUP

**Nicotinamide**

**Gastrointestinal** Nicotinamide has been recommended for the control of hyperphosphatemia in patients on dialysis; *diarrhea* occurred in a small proportion (7.8%) of patients in this study. [4C]. The preliminary observations from a prospective, open trial to test this proposal,
using high doses of nicotinamide, have been reported [5^A]. Five of six patients on hemodialysis developed diarrhea after receiving nicotinamide in a mean dosage of 1050 mg/bag. The diarrhea stopped when the nicotinamide was withdrawn or the dose reduced (from a mean of 85 mg/l to 54 mg/l). The authors speculated that the higher incidence of diarrhea they observed may have been linked to the simultaneous use of calcium carbonate and/or a phosphate binder, the latter being excluded from the original study.

VITAMIN C (Ascorbic acid) [SED-15, 351; SEDA-30, 394]

**Urinary tract** One risk associated with large doses of ascorbic acid is the formation and deposition of calcium oxalate crystals in the kidneys, as reported in an case of extreme oral vitamin C dosage [6^A].

{Case report starts}

- A 49-year-old woman, who had taken vitamin C at least 4 g/day for several months, developed acute oliguric renal failure and a creatinine of 400 μmol/l (4.5 mg/dl). She had a history of migraine, for which she had been taking large doses of ibuprofen (up to 2000 mg/day). She also reported nausea and vomiting over the previous 24 hours. She had orthostatic hypotension and dry mucous membranes. There was marked proteinuria. Renal biopsy showed widespread tubular degenerative changes and interstitial edema, typical of acute tubular necrosis, with prominent tubular calcium oxalate deposition. The glomeruli were unremarkable. She became anuric, received four hemodialysis treatments, and began to recover renal function. Nine months later, her creatinine concentration was 97 μmol/l (1.1 mg/dl).

{Case report ends}

The authors conclude that acute tubular necrosis observed in this patient was most likely related to dehydration and renal hypoperfusion in the setting of nausea, vomiting and the use of high doses of non-steroidal anti-inflammatory drugs. Calcium oxalate deposition was presumably related to the very high vitamin C intake, since oxalate results from its metabolism.

**Pregnancy** See vitamins above.

VITAMIN D ANALOGUES [SED-15, 3669; SEDA-28, 388; SEDA-29, 354; SEDA-30, 394]
Mineral balance Absorption of calcium carbonate in the fasting state has been reported to be significantly compromised in subjects with achlorhydria. Although calcium carbonate malabsorption in the fasting state cannot be predicted, it might be corrected if the compound were administered with meals. However, administering calcium carbonate with meals is logistically challenging in long-term care facilities. A woman who was switched to calcium citrate subsequently had severe symptomatic hypercalcemia [7].

{Case report starts}

- An 89-year-old woman, resident in the Wisconsin Veterans Home, a skilled nursing facility, was taking long-term ergocalciferol (vitamin D2) 50 000 IU/day and calcium carbonate supplements in the morning, and rarely ate breakfast. She was switched from calcium carbonate 2000 mg/day to calcium citrate 1230 mg/day, after which she developed severe symptomatic hypercalcemia (4.2 mmol/l).

{Case report ends}

The authors concluded that the primary cause of hypercalcemia in this case was the administration of an inappropriately high dose of vitamin D, manifested when calcium carbonate was replaced with calcium citrate.

The management of hypercalcemia in children as a result of vitamin D intoxication, is usually with intravenous bisphosphonates, such as pamidronate. Oral alendronate can also be used [8].

{Case report starts}

- A 7-year-old boy developed classic symptoms of vitamin D intoxication after taking oral vitamin D (colecalciferol) 300 000 units/day for 15 days to treat suspected vitamin deficiency. There was turgor of the skin and dryness of the oral mucosa, consistent with moderate dehydration. Intravenous rehydration was begun and dietary calcium and vitamin D were restricted. The serum calcium concentration on day 2 was 4.7 mmol/l. The urinary calcium/creatinine ratio was initially high. Alendronate sodium 5 mg/day was given by mouth. The serum calcium fell slightly to 3.6 mmol/l on day 3, and the dose was increased to 10 mg/day. By day 16, the serum calcium had fallen to 2.6 mmol/l and treatment was withdrawn. The urinary calcium/creatinine ratio fell gradually to normal over 2 months.

{Case report ends}
This case suggests that oral bisphosphonates can be used to treat the effects of vitamin D intoxication. It also provides some pointers to dose and duration of treatment. The authors recommended that patients treated with a bisphosphonate in this way should be followed-up closely for several years.

VITAMIN E [SED-15, 3677; SEDA-29, 355; SEDA-30, 395]

Pregnancy See vitamins above.

PARENTERAL NUTRITION [SED-15, 2700; SEDA-28, 383; SEDA-29, 353]

Nutrition There has been yet another report of Wernicke’s encephalopathy associated with thiamine deficiency in a patient receiving parenteral nutrition, due to failure to include multivitamins in the regimen [9^].

{Case report starts}

- A 30-year-old woman developed peritonitis and a digestive tract fistula after elective surgery for a benign gastric tumor. She was given parenteral nutrition and antimicrobial drugs. After 30 days, she reported fatigue. Hyponatremia and hypophosphatemia were corrected, but she became stuporose and was intubated and ventilated. Micronutrients (multivitamins and trace elements) were added. After 3 days, her neurological status improved, allowing extubation, but she had horizontal nystagmus and a lateral ophthalmoplegia. An MRI scan showed no sign of central pontine myelolysis but hyperintense lesions in the medial thalami. Thiamine was increased to 200 mg/day and the oculomotor signs and MRI scans regressed. However, a severe cognitive deficit with vertigo and loss of sphincter control persisted for at least 2 years. She remained totally dependent and disorientated with memory disturbances.

{Case report ends}

While the authors emphasized the difficulties in diagnosing Wernicke’s encephalopathy, this case clearly illustrates yet again the dangers of omitting micronutrients from parenteral nutrition. It also shows that the commonest manifestation of vitamin deficiency in parenteral nutrition when micronutrients have been excluded is likely to be thiamine deficiency, as has been previously reported. It has also provided some indication of the approximate time before such symptoms become evident.
**Susceptibility factors Blood glucose** The effects of total parenteral nutrition-associated hyperglycemia on clinical outcomes in premature septic infants in the neonatal intensive care unit have been investigated [10]. The charts of all premature infants weighing less than 1500 g with sepsis, ventilator dependence, and feeding intolerance were studied; there were 37 of them. The average caloric intake at the time of blood culture-proven sepsis was 83 kcal/kg/day. The maximum serum glucose concentration correlated positively with the duration of total parenteral nutrition, length of dependence on mechanical ventilation, and hospital length of stay. The average maximum serum glucose concentration was significantly higher in the non-surviving infants (13.4 versus 7.8 mmol/l). The tentative conclusion is that avoidance of excessive nutrient delivery and tight glycemic control during periods of acute metabolic stress may improve outcome in these patients.

**Fat emulsions**

**Liver Cholestasis** is one of the most serious complications of parenteral nutrition in infants. Recently introduced fat emulsions containing fish oils, in particular omega-3 fatty acids, may be beneficial in reducing the incidence of liver-associated complications. Two infants with intestinal failure and parenteral nutrition-associated liver disease were given an intravenous fat emulsion containing primarily omega-3 fatty acids instead of the conventional emulsion [11]. Biochemical tests of liver function improved significantly. One child was removed from the liver transplantation list because of improved hepatic function, and the second child had complete resolution of cholestasis while solely on parenteral nutrition. This suggests that fat emulsions made from fish oils may be effective in treating and preventing this often fatal condition. A randomized, controlled trial is necessary.

**Vitamins**

See vitamins above.

**References**

{In endnotes}


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