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Carnitine deficiency associated with long-term pivampicillin treatment: the effect of a replacement therapy regime

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Summary: A 51 year old female developed a skeletal muscle myopathy after 3 months of pivampicillin therapy. Pivampicillin can cause carnitine deficiency due to the pivalic acid side group. Plasma carnitine content and the patients symptoms failed to improve significantly on discontinuing the drug. Oral carnitine replacement therapy was administered for 6 weeks but the patient's plasma carnitine levels responded only slowly to this treatment. It is suggested that pivampicillin inhibits uptake of carnitine from the gut and may either directly or indirectly depress endogenous carnitine synthesis. In such cases a more aggressive carnitine replacement regime is indicated and pivampicillin should be avoided in patients requiring long-term antibiotic administration.

Introduction

Carnitine is an essential co-factor for the use of fatty acids as a metabolic fuel.[1] Abnormally high plasma carnitine content is associated with liver disease[2,3] whilst carnitine deficiency has been reported to cause skeletal myopathy, cardiomyopathy, vomiting, encephalopathy, hepatomegaly, hypoketotic glycaemia and a Reye's-like syndrome.[4] Pivampicillin is known to cause carnitine deficiency in some cases through the action of pivalic acid which is conjugated to the penicillin moiety to increase absorption.[5] In this study we report a patient with skeletal myopathy and severe carnitine deficiency following long-term pivampicillin treatment.

Case report

A 51 year old woman presented with a 6 month history of feeling unwell. Examination showed an enlarged spleen and splenic cyst. The spleen was removed and was found to contain granulomatous sarcoid with negative Ziehl-Nielson stain and negative culture for acid-alcohol fast bacilli. She was commenced on prednisolone with some improvement in her well-being. Ampicillin was given for 2 months as anti-pneumococcal prophylaxis, but for the patient's convenience, pivampicillin at a dose of 250 mg twice daily, was substituted. Three months after starting pivampicillin the patient complained of lethargy, muscle weakness and wasting, weight loss and poor appetite. Extensive investigations could not account for these symptoms. After 5 months of pivampicillin therapy, urinary and plasma carnitine levels were measured,[6] and were found to be much lower than the normal range (see Table I). Pivampicillin treatment was discontinued and plasma and urine carnitine content were measured at intervals of 10 days and 2 months after the cessation of treatment and were found to have remained very low, although the patient had gained weight and her muscle bulk and power improved to some extent. The patient was treated with oral L-carnitine supplements, 1 g daily. There was further clinical improvement but plasma and urine carnitine content did not approach the normal range until after six weeks of treatment.

Discussion

Sepsis following splenectomy, caused by organisms such as *Streptococcus pneumoniae, Neisseria meningitis, Escherichia coli* and *Haemophilus influenzae*, is a well-recognized complication of the operation.

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Table I Plasma and urine carnitine content during pivampicillin treatment and carnitine replacement therapy

	During pivampicillin therapy	*Ten days after stopping pivampicillin*	*Two months after stopping pivampicillin*	*Post one week course carnitine*	*Post six week course carnitine*	*Normal range*
Plasma levels (nmol/ml)						
Free carnitine	5.4	4.6	2.0	1.8	13.1	22–50
Short-chain esters	<1.0	0.7	<1.0	<1.0	8.2	3.5–10
Long-chain esters	2.6	3.0	2.9	0.7	2.6	0.6–2
Total carnitine	9.0	8.3	5.9	3.5	23.9	30–60
Urine levels (nmol/mg creatinine)						
Free carnitine	16.1	35.1	4.8	0.0	<1.0	0–500
Short-chain esters	22.5	14.1	17.8	18.6	72.5	100–4000
Total carnitine	38.6	49.2	22.6	18.6	73.5	100–4500
Patients weight (kg)	58.0			62.0	62.5	

Whilst there is doubt about the efficacy of anti-pneumococcal vaccines after splenectomy, particularly in immunocompromised patients, daily prophylactic penicillin adminstered for at least 2 years postoperatively has been found to be highly effective in preventing infection.[7] In some cases, administration of pivampicillin has been shown to result in an immediate decrease in plasma carnitine content coupled with its excretion in the urine as pivaloylcarnitine,[8] due not to the antibiotic action of the drug but to the metabolism of the stabilizing pivalic acid group. This particular patient had been taking pivampicillin for 3 months before symptoms occurred. We have not found reports of other patients with severe carnitine deficiency presenting with symptoms of myopathy following long-term pivampicillin treatment.

The most surprising finding from this case study was the very long period for which carnitine deficiency persisted. Two months after the cessation of pivampicillin treatment, plasma total carnitine content was only 17% of the accepted normal value and had fallen significantly from the levels recorded during the administration of the antibiotic. Excretion of free carnitine in urine also fell during this period whilst the amount of short-chain esters excreted was maintained at a low but relatively constant level. Seven grams of carnitine taken orally over one week had no effect on raising the patient's very low plasma and urinary levels to normal values, and even after 6 weeks of this replacement regime plasma and urine carnitine content remained at the lower end of the normal range. In normal humans such an intake of carnitine leads to large increases in the plasma content.[9] If, in this patient carnitine was being taken up in the gut at a normal rate, we would have expected to see increased urinary excretion as well as increased plasma content. This was not the case and leads us to suggest that at least one effect of pivalic acid is to inhibit carnitine uptake by this route. The body can synthesize its requirement for carnitine, however, the substrate for this process is trimethyllysine incorporated into protein. Since when pivampicillin was discontinued carnitine levels remained depressed, we also conclude that endogenous synthesis cannot make good the carnitine deficiency. This could be an indirect effect of pivalic acid rather than a direct action as the body is unlikely to tolerate the extent of protein breakdown required for endogenous carnitine biosynthesis for sustained periods.

Carnitine is well tolerated and doses of up to 15 g/day can be administered orally without serious side effects.[10] We suggest that in similar cases more intensive oral carnitine replacement regime with, for example, 5 g/day or an intravenous administration regime is indicated. Pivalic acid derivatives of ampicillin are used to increase absorption, but should probably be avoided in patients requiring long-term administration.

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