

Ketogenic dietary therapy and anti-epileptic medications

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Ketogenic dietary therapy includes the classical ketogenic diet (KD), the medium chain triglyceride KD, the modified Atkins diet (MAD) (or variants which may be termed modified KD) and the low glycaemic index treatment. Many studies, including randomised trials, have reported reduced seizure frequency and severity in children and adults on these dietary therapies. They are usually used to treat intractable seizures which have not responded to appropriate medication so most who start them will be on at least one concurrent anti-epileptic drug (AED); a reduced dependence on AEDs being a goal and frequently attained outcome of ketogenic dietary therapy. This insight reviews the literature and discusses evidence for any interaction between these diets and AEDs.

1. Does ketogenic dietary therapy affect blood levels of AEDs?

Four studies have examined this question. The first measured plasma levels of valproic acid (VPA), lamotrigine, topiramate, clonazepam and phenobarbital in 51 children on classical KD. Although some AED doses were adjusted, no significant effect on plasma concentrations was seen after three months on the diet and the authors concluded it is not necessary to adjust drug doses due to pharmacokinetic interactions when starting the KD (1). Another study measured plasma levels of VPA and phenobarbital in 36 children and adolescents after one month on classical KD given as a ketogenic formula either on its own or providing 80% of diet intake. Doses of AEDs were not changed during the month (although some patients had concomitant benzodiazepine doses changed during this time). Concentrations of phenobarbital did not change but VPA showed a slight but not significant decrease (2). A group of four adults had AED levels measured after four and 12 weeks on MAD. Combinations of two or three AEDs were used including carbamazepine, clobazam, lamotrigine, nitrazepam, oxcarbazepine, VPA, zonisamide, and topiramate; no changes to AEDs were made during the diet period. After 12 weeks average serum AED concentrations were reduced by 35% compared to pre-diet values (3). A review of 139 children who had been on either classical KD or MAD for over a month reported a decrease in concentrations of carbamazepine, lamotrigine, levetiracetam, topiramate and VPA, with a small increase in phenobarbital. Only the change in VPA reached statistical significance and the effect of different diet variants was not studied; the authors recommended that concentrations of VPA should be monitored when used alongside ketogenic dietary therapy (4).

2. Is there increased risk of side effects when using ketogenic dietary therapy in combination with AEDs?

Kidney stones and metabolic acidosis are reported side effects of the KD and the carbonic anhydrase inhibitor AEDs topiramate and zonisamide; it has been suggested that their concurrent use could further increase risk. One study of 14 children on both topiramate and classical KD did see a decrease in bicarbonate levels in most children, mainly at diet initiation, however none developed kidney stones (5). A review of 301 children started on classical KD found no difference in kidney stone incidence between 80 who were on topiramate or zonisamide and the rest of the KD

group (6). Results from a cohort of 195 KD children reported 13 developed kidney stones as a side effect but the prevalence did not correlate with use of topiramate or zonisamide (7). Conversely, a review of 93 children on KD reported that six developed kidney stones, of whom three were also on zonisamide and one on topiramate (8). Many centres will recommend a renal ultrasound in children starting the KD who are already on topiramate or zonisamide and adequate fluid intake should be encouraged, some centres will routinely prescribe a urine alkalinising agent such as potassium citrate. Careful monitoring at diet initiation is needed in this group due to the increased risk of acidosis.

There have been suggestions that concurrent treatment with VPA may increase risk of KD complications. In a prospective study of 52 children on classical KD, five developed serious complications of whom four were also on VPA; these resolved in three children once VPA was discontinued with carnitine deficiency suggested as one possible mechanism (9). Carnitine has an essential role in fat metabolism so requirements may be increased on a high fat diet. Although deficiency is rare, risk is increased by use of multiple AEDs (10). A case report has also been published of an 18-year-old female who developed hepatitis while on the KD which resolved after stopping VPA (11). A further study examined the combined use of KD and VPA in 75 children; the authors concluded that in most cases their co-administration was safe, but two children developed side effects with an increase in ketosis once VPA was removed (12).

3. Could concurrent use of AEDs influence the efficacy of ketogenic dietary therapy?

This question has been studied in a retrospective review of 115 children on KD who had no AED changes during the first three months of diet therapy. The influence of levetiracetam, lamotrigine, phenobarbital, topiramate, VPA and zonisamide on three-month diet efficacy was analysed. Children on phenobarbital in combination with KD were significantly less likely to have over 50% seizure reduction whereas those on zonisamide in combination with KD were more likely to have over 50% seizure reduction (13). Another study of 71 children starting KD found significantly reduced three-month diet efficacy in 16 children who were on concurrent lamotrigine compared other AEDs (14). Further trials will be needed to examine this question in more detail.

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