Topiramate: Pharmacokinetics and Pharmacodynamics

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ABSTRACT: Topiramate is a structurally novel anti-epileptic drug with at least 3 postulated mechanisms of action including: 1) potentiation of GABA responses, 2) impairment of AMPA/kainate glutamate receptors and 3) suppression of high frequency action potential firing. It has a favourable pharmacokinetic profile with rapid absorption, good bio-availability, linear pharmacokinetics, relatively long half-life and limited pharmacokinetic drug interactions. However, topiramate can reduce the estrogen component of oral contraceptive medications. Women may require birth control preparations containing 50 μg of estrogen. Topiramate clearance is reduced in severe renal failure and increased by enzyme-inducing anti-epileptic drugs. The dose of topiramate may have to be reduced in renal failure or when withdrawing enzyme inducers.

RÉSUMÉ: Pharmacocinétique et pharmacodynamique du topiramate. Le topiramate est un médicament antiépileptique dont la structure est nouvelle et pour lequel on postule au moins trois mécanismes d'action dont: 1) la potentiation des réponses GABAergiques; 2) le blocage des récepteurs au AMPA/kainate glutamate et 3) la suppression de la décharge du potentiel d'action de haute fréquence. Il a un profil pharmacocinétique favorable avec une absorption rapide, une bonne biodisponibilité, une pharmacocinétique linéaire, une demi-vie relativement longue et peu d'interactions pharmacocinétiques médicamenteuses. Cependant, le topiramate peut diminuer l'efficacité des oestrogènes des contraceptifs oraux. Les femmes peuvent avoir besoin de contraceptifs oraux contenant 50 μg d'oestrogènes. La clairance du topiramate est diminuée dans l'insuffisance rénale sévère et augmentée par les antiépileptiques qui sont des inducteurs enzymatiques. La dose de topiramate doit être diminuée dans l'insuffisance rénale ou quand on cesse un inducteur enzymatique.

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Epileptic seizures can often be controlled with available drugs; however, at least 25-30% of patients continue to suffer from seizures or have intolerable side effects. Standard anti-epileptic drugs (e.g., phenytoin, carbamazepine, barbiturates, sodium valproate) have pharmacokinetic properties which can produce complex drug interactions which limit their use. New drugs with novel mechanisms of action and more favourable pharmacokinetic profiles are needed in order to improve seizure control while minimizing side effects. This review will focus on the mechanisms of action and pharmacokinetics of topiramate which was introduced in Canada for treatment of epilepsy in 1997.

Topiramate (2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate) has a novel chemical structure. It is a sulfamated derivative of fructose, a naturally occurring monosaccharide.

Mechanisms of Action

Topiramate has been shown to be effective in several animal models of epilepsy, including: maximal electroshock seizures in rats and mice;[1] tonic and absence seizures in spontaneous epileptic rats; clonic and tonic seizures in DBA mice;[2] stroke epilepsy in rats;[2] and kindled seizures in rats.[4] It elevates the seizure threshold but does not block the seizures induced by subcutaneous pentylenetetrazole.[1] These pre-clinical studies suggested that topiramate might have a broad spectrum of action against multiple seizure types including partial, generalized tonic-clonic seizures and perhaps absence.

The mechanisms of anticonvulsant action of topiramate are still not fully understood. Although its sulfamate group suggested that topiramate might be a carbonic anhydrase inhibitor, its effects on carbonic anhydrase are weak and not thought to be one of its major mechanisms of anti-convulsant action.[1] However, preliminary studies suggest that three potential mechanisms might contribute to the anti-convulsant effect.

Topiramate reversibly blocks sustained repetitive action potential firing in hippocampal pyramidal neurons.[5] The effect is similar to those of state-dependent sodium channel blockers, such as phenytoin and carbamazepine.

Topiramate has been shown to enhance chloride flux and to potentiate $GABA_A$ currents.[6] The mechanism of $GABA_A$ potentiation appears similar to that of benzodiazepines with an increase in the frequency of channel opening, but no increase in open time duration.[7] However, this action is not mediated through the benzodiazepine site on the $GABA_A$ channel since it was not inhibited by the benzodiazepine antagonist, flumazenil.[7]

Topiramate has been shown to reduce inward kainate-evoked

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currents in hippocampal neurons.[8] It has no effect on NMDA induced responses. Although blockade of sodium channels and enhancement of $GABA_A$ responses are mechanisms which topiramate shares with other anti-epileptic drugs, the selective blockade on the AMPA/kainate subtype of glutamate receptors is unique among anti-epileptic drugs and opens up new targets for anti-epileptic drug development (Table 1).

Table 1: Proposed Actions of Topiramate.

Limits repetitive firing by blocking voltage-dependent sodium channels
Enhances $GABA_A$ receptor mediated inhibition
Blocks AMPA/kainate glutamate receptors
Weak carbonic anhydrase inhibitor.

Pharmacokinetics

Topiramate has a favourable pharmacokinetic profile (Table 2). It is rapidly absorbed with peak serum levels occurring 1-4 hours after an oral dose.[9,10] Bio-availability exceeds 80% following an oral dose and is not significantly affected by food.[10] Plasma concentrations are linearly related to dose.[10] Protein binding is negligible (9-17%).[11]

The clearance of topiramate can be reduced in patients with severe renal impairment by up to 54%.[12] This can result in significant increases in plasma topiramate levels. When renal function is significantly impaired, the topiramate dose may have to be reduced.

Topiramate is not extensively metabolized with 75-80% of the drug excreted unchanged in the urine[10] when given in monotherapy. Severe hepatic failure may result in moderate increases in plasma topiramate levels, however, these are usually not clinically significant. The elimination half-life is between 20-30 hours in the absence of enzyme-inducing agents[10] making it suitable for once or twice daily dosing schedule. However, enzyme inducers (e.g., phenytoin, carbamazepine or phenobarbital) can increase metabolism up to 50% and reduce the half-life to 12-15 hours[13,14] (Table 3). Side effects occurring during withdrawal of concomitant enzyme-inducing anti-epileptic drugs may be due to rising topiramate levels. Topiramate dose reductions may be necessary. Valproate has no significant effect on topiramate clearance.[15] Phenytoin concentrations may be up to 20% higher in patients taking topiramate especially when multiple doses of phenytoin are used[13] (Table 3). However, the effects on phenytoin were not considered to be clinically significant. Topiramate has no significant effect on carbamazepine or valproate concentrations.[14,15]

Table 2: Clinically Useful Pharmacokinetic Parameters.

Parameter	Clinical implication
Absorption T_{max} 1-4 hrs	Rapid oral absorption
Bioavailability not significantly affected by food	Can be taken with food
Negligible protein binding (9-17%)	No protein binding interactions
Linear pharmacokinetics	Predictable change in blood level with dosage change
Eliminated predominantly by renal excretion	Dose may have to be reduced in renal failure
Little hepatic metabolism	Dosage adjustment not usually required with hepatic impairment; no active metabolites
Half-life 20-30 hr	Can use once or twice daily dosing schedule; improved compliance.

Table 3: Effects of Standard Anti-epileptic Drugs on Topiramate.

Drug	Effect on Topiramate concentration
Phenytoin	decrease
Carbamazepine	decrease
Phenobarbital	?decrease (not studied)
Valproic acid	no effect

Topiramate can reduce the plasma estrogen levels by up to 30% in women taking oral contraceptives[16] (Table 4). Women should be warned of the potential for reduced efficacy of oral contraceptives and advised to either use alternative forms of contraception or be prescribed oral contraceptives containing higher estrogen content (e.g., 50 μg).

There is limited experience with interactions with other medications. However, potential interactions have been explored using an *in-vitro* model with various human cytochrome P450 isoforms.[17] These results suggest that topiramate would have no inhibitory effects on neuroleptics, tricyclic anti-depressants, caffeine, theophylline or coumadin.

Pharmacokinetic parameters in the elderly are similar to those in younger adults. Dosage adjustments in the elderly are generally not required unless there is significant renal impairment.

Table 4: Effects of Topiramate on Other Drugs.

Drug	Effect of Topiramate on drug concentration
Phenytoin	increase ~20%
Carbamazepine	no effect
Phenobarbital	?
Valproic acid	no effect
Oral contraceptive	decrease.

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